

MGIPC-S4-10 AR-21649-1,000.

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1947. Part II., pp. 881-1709.

LONDON: THE CHEMICAL SOCIETY.

1947.

PRINTED IN GREAT BRITAIN BY
RICHARD CLAY AND COMPANY, LTD.,
BUNGAY, SUFFOLK.

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386	6*	for "(2.65 g. or 48%)" read "(5.15 g., 93%)"
388	28	for " <i>N</i> -benzyl- <i>N'</i> -methylbenzamidine" read " <i>N</i> -Benzyl- <i>N'</i> -methylbenzamidine".
499		In the last line of the formulæ, for " $= p\text{-Me}\cdot\text{C}_6\text{H}_4$ " read " $(\text{T} = p\text{-Me}\cdot\text{C}_6\text{H}_4)$ ".

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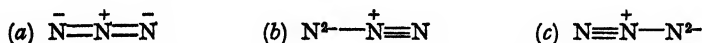
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164. The Crystal Structure of Strontium Azide.

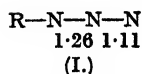
By F. J. LLEWELLYN and F. E. WHITMORE.

The structure of strontium azide has been completely determined by means of three-dimensional Fourier sections and lines using all the $\{hkl\}$ structure amplitudes obtainable with Cu- $K\alpha$ X-radiation. The structure is ionic, each strontium ion being surrounded by 8 azide ions, arranged in two sets, at distances 2.63 and 2.77 Å., severally. The azide ion is linear and symmetrical, the nitrogen-nitrogen separation being 1.12 Å.

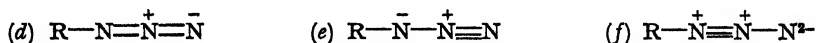
THE azide grouping (N_3) has been shown by X-ray and electron-diffraction studies to be linear in both electrovalent and covalent substances. In the former, typified by sodium and ammonium azides (Frevel, *J. Amer. Chem. Soc.*, 1936, 58, 779; *Z. Krist.*, 1936, 94, A, 197) the two nitrogen-nitrogen separations in the azide ion are equal; the ion resonates between the three structures (a), (b), and (c),



each of which is equally important, and stabilisation is effected by the considerable resonance energy; the nitrogen-nitrogen separation is 1.15 Å. In the latter case, typified by cyanuric triazide (Knaggs, *Proc. Roy. Soc.*, 1935, 150, A, 576), these two nitrogen-nitrogen bonds are not equivalent and the azide grouping has the dimensions shown in (I).



The three most probable resonance forms for the covalently linked azide group are (d), (e), and (f):



the last probably does not contribute to any appreciable extent, for it involves adjacent positive charges which render this form more unstable. Resonance therefore occurs between (d) and (e), leading to an unsymmetrical grouping of lower stability than the azide ion.

The stability of metallic azides to heat, friction, and impact varies considerably and is determined, at least in part, by the bonding between the metal and the azide group. Thus, the alkali-metal azides, which are ionic, are stable both to friction and to impact and are only decomposed gently by heat at 300–400°. The alkaline-earth azides are decomposed more violently by heat at a lower temperature (*ca.* 110–160°) but remain insensitive to friction and impact. On the other hand, azides of the heavier metals, *e.g.*, lead, and those of many of the B-sub-group elements, *e.g.*, copper and silver, decompose sometimes with explosive violence when lightly struck or rubbed.

Between these two extremes there is a large number of azides of intermediate properties in which it may be assumed that the linkage of the azide group is more or less covalent. The following investigation of the structure of strontium azide is the first of a series in which it is hoped to trace the development of covalent bonding with increasing instability.

Preliminary Crystallographic Data.—Small, well-defined, orthorhombic, bipyramidal (pseudo-tetragonal) crystals of strontium azide exhibiting the form $\{111\}$ were obtained by slowly evaporating the aqueous solution to dryness in an Erlenmeyer flask. Single-crystal rotation photographs using Cu- $K\alpha$ X-radiation gave the cell dimensions: $[a] = 11.82$, $[b] = 11.47$, $[c] = 6.08$ Å. Oscillation photographs about the three principal axes revealed the halvings $\{hkl\}$ absent when $h + k \neq 2n$, $h + l \neq 2n$, $k + l \neq 2n$; $\{0kl\}$ absent when $k \neq 2n$, $l \neq 2n$, $k + l \neq 4n$; $\{h0l\}$ absent when $h \neq 2n$, $l \neq 2n$, $h + l \neq 4n$; and $\{hkh0\}$ absent when $h \neq 2n$, $k \neq 2n$, $h + k \neq 4n$. The space-group is therefore F_{dd} . The observed density is 2.73 g./c.c.; calculated for eight molecules in the unit cell, 2.77 g./c.c.

The space-group F_{dd} accommodates 32 general positions, five sets of 16-fold special positions, and two sets of 8-fold special positions. Since there are 8 strontium ions in the unit cell, these must be located in one of the sets of 8-fold special positions, and because the choice between these is arbitrary, the co-ordinates may be written down as (000), $(0\frac{1}{2}\frac{1}{2})$, $(\frac{1}{2}0\frac{1}{2})$, $(\frac{1}{2}\frac{1}{2}0)$, $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$, $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$, $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$, $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$.

The azide grouping can conveniently be dealt with in two parts: (a) the central nitrogen atoms, of which there are 16, must lie in one of the 16-fold special positions; and (b) the end nitrogen atoms, of which there are 32 located in the general positions, or in two sets of 16-fold positions.

(a) The five sets of 16-fold positions can be classified into two kinds; the first is centro-

symmetrical, and the second possesses two-fold axial symmetry. Thus, whatever the actual position of the azide group, it must possess either a centre of symmetry or a two-fold axis.

Measurement of Intensities.—The intensities of the diffracted beams from all the planes $\{hkl\}$ observed by using Cu-K α X-radiation were obtained by visual estimation using a simple comparator on which a number of photographic spots produced by beams of known intensity had previously been recorded. From these intensities a set of structure amplitudes, on an arbitrary scale, can be obtained by using the relation $F = k\sqrt{IDp/L}$, the symbols of which are defined in an earlier paper (this vol., p. 838).

Usually it is convenient to render a set of relative structure amplitudes absolute by comparing directly a number of diffracted beams with some standard beam—normally the 400 reflection from the ground cleavage face of rock-salt. In this particular case we did not consider this to be necessary since the phases of nearly all the structure amplitudes could be deduced from the known position of the strontium atoms. When the structure was completed, the experimental structure amplitudes were made absolute by multiplying by the factor $F_{\text{calc.}}/F_{\text{obs.}}$. The table includes a list of the experimental structure amplitudes and also the calculated phases and structure amplitudes.

<i>hkl.</i>	<i>F</i> _{calc.}	<i>F</i> _{obs.}	<i>hkl.</i>	<i>F</i> _{calc.}	<i>F</i> _{obs.}	<i>hkl.</i>	<i>F</i> _{calc.}	<i>F</i> _{obs.}
004	123	169	335	45	93	711	37	99
022	278	250	351	62	124	713	86	112
026	273	184	353	140	167	715	39	69
040	347	268	355	141	122	731	12	66
044	224	188	371	117	133	733	98	104
062	296	239	373	121	143	735	16	95
066	140	118	375	60	84	751	128	108
080	99	161	391	69	120	753	35	55
084	311	195	393	123	114	755	0	37
0, 10, 2	246	186	395	36	65	771	50	99
0, 12, 0	157	173	3, 11, 1	43	83	773	48	57
111	62	114	3, 11, 3	118	85	791	67	81
113	118	152	3, 13, 1	120	95	793	33	49
115	65	97	400	-71	<20	7, 11, 1	96	116
117	65	58	404	217	177	800	417	309
131	55	58	422	156	160	804	107	116
133	109	142	426	22	81	822	211	179
135	93	119	440	100	148	840	260	188
151	128	175	444	103	107	842	192	124
153	28	73	462	73	114	862	238	172
155	4	62	480	233	199	880	88	142
171	120	138	484	-22	56	8, 10, 2	216	144
173	83	79	4, 10, 2	48	98	911	16	91
175	25	81	4, 12, 0	115	88	913	97	95
191	79	118	511	193	168	915	34	73
193	46	76	513	76	113	931	10	67
195	47	73	515	110	115	933	76	82
1, 11, 1	92	118	531	199	191	935	56	85
1, 11, 3	70	63	533	107	110	951	72	102
1, 13, 1	10	46	535	69	83	953	19	48
202	233	208	551	89	98	971	63	95
206	155	144	553	142	140	973	-21	134
220	285	250	555	127	111	991	70	86
222	124	100	571	99	112	10, 0, 2	172	151
224	132	184	573	143	123	10, 2, 0	247	152
242	211	188	575	78	64	10, 2, 4	130	113
246	143	127	591	73	106	10, 4, 2	180	115
260	195	191	593	143	94	10, 6, 0	142	148
262	130	59	5, 11, 1	87	80	10, 8, 2	133	123
264	168	150	602	183	184	11, 1, 1	73	114
282	174	173	606	89	138	11, 1, 3	72	73
2, 10, 0	144	165	620	134	248	11, 3, 1	134	113
2, 10, 4	148	109	622	-101	60	11, 3, 3	53	64
2, 12, 2	140	110	624	161	146	11, 5, 1	127	71
311	164	228	642	156	150	11, 7, 1	94	97
313	86	124	646	113	127	12, 0, 0	-14	44
315	114	219	660	176	177	12, 2, 2	66	107
317	115	120	682	118	150	12, 4, 0	87	97
331	214	232	6, 10, 0	153	152	13, 1, 1	132	96
333	76	121	6, 10, 2	153	152	13, 3, 1	120	94

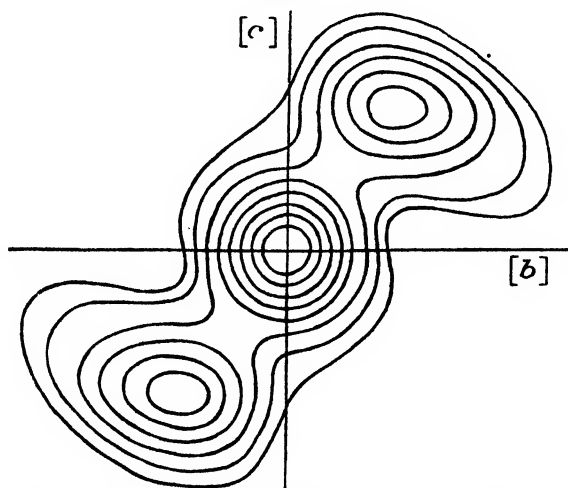
Determination of the Structure.—The strontium atoms located at (000), etc., will be in phase and contribute to all the observed $(h\bar{h}0)_x$, $(h0l)$, and $0kl$ planes. Since the contributions of the

strontium atoms will in general be greater than that of the nitrogens, as a first approximation, the phase of these planes was taken as 0° , or, in other words, these structure amplitudes are positive. A Fourier projection on the c -plane using all the $hk0$ structure amplitudes was therefore computed in order to determine the approximate co-ordinates of the atoms of the azide group. Two peaks were observed having (xy) co-ordinates $(0.125, 0.000)$ and $(0.125, 0.075)$. It therefore appeared likely that the central nitrogen atom was located on the two-fold axis which passes through the origin and is parallel to the $[a]$ axis. That the atoms of the azide group have x co-ordinates approximately equal to 0.125 is indicated by the relative magnitudes of F_{400} — very small, F_{800} — very large, F_{1200} — very small; F_{h00} being calculable by the equation

$$F_{h00} = 8f_{\text{Sr}} + 16f_{\text{N centre}} \cos 2\pi hx + 32f_{\text{N}} \cos 2\pi hx$$

Having thus established that the central nitrogen atom lies along the $[a]$ axis, two possibilities arise: the peak observed at (xy) co-ordinates $(0.125, 0.000)$ may be due to an atom having (xyz) co-ordinates $(0.125, 0.000, 0.000)$ leading to the 16 positions $(0.125, 0.000, 0.000)$, $(-0.125, 0.000, 0.000)$, $(0.375, 0.250, 0.250)$, $(0.125, 0.250, 0.250)$, $(0.125, 0.500, 0.500)$, $(-0.125, 0.500, 0.500)$, $(0.375, 0.750, 0.750)$, $(0.125, 0.750, 0.750)$, $(0.625, 0.000, 0.500)$, $(0.375, 0.000, 0.500)$, $(0.875, 0.250, 0.750)$, $(0.625, 0.250, 0.750)$, $(0.625, 0.500, 0.000)$, $(0.375, 0.500, 0.000)$, $(0.875, 0.750, 0.250)$, $(0.625, 0.750, 0.250)$, or to an atom at $(0.375, 0.000, 0.000)$ leading to 16 positions as above. It will be readily seen that these two possibilities reduce to the same set of (xy) co-ordinates.

FIG. 1.



The atomic co-ordinates $(0.125, 0.000, 0.000)$ for the central nitrogen are extremely improbable since the separation from the strontium atom at the origin would then be only 1.47 \AA , considerably less than the sum of the Sr^{2+} and N^- radii. Attention was therefore directed to the other possibility in which the two nitrogen atoms have the approximate co-ordinates

$$\text{N}_1 \text{ centre } 0.375 \quad 0 \quad 0 \quad \text{N}_2 \quad 0.375 \quad y \quad z$$

The three-dimensional Fourier line, parallel to the $[a]$ axis, passing through the point $x = 0$, $y = 0$ showed a large maximum at $z = 0.375$. A three-dimensional Fourier section parallel to the a -plane at a height $z = 0.375$ led to (yz) co-ordinates $(0.075, 0.083)$ for the terminal nitrogen atom of the azide group. Further, three-dimensional Fourier lines and sections were then computed in order to refine these co-ordinates; during this process only a small number of those structure amplitudes towards which the strontium atoms contribute changed sign, but there was a general rearrangement in those for which the strontium contribution is zero. The final co-ordinates, derived from the Fourier section shown in Fig. 1 and the three-dimensional Fourier lines parallel to the $[a]$ axis, are:

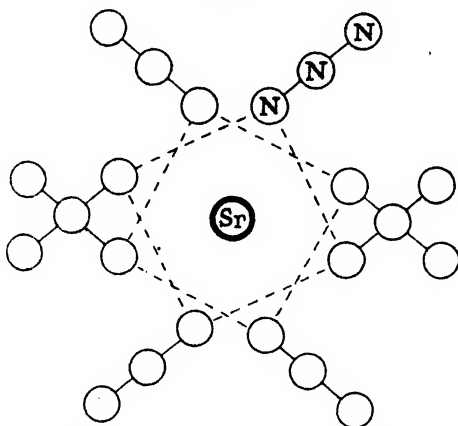
$$\text{Sr } 0 \quad 0 \quad 0 \quad \text{N}_1 \quad 0.383 \quad 0 \quad 0 \quad \text{N}_2 \quad 0.383 \quad 0.058 \quad 0.148$$

The agreement between the observed and the calculated structure amplitudes (the average discrepancy is 27%) is not of the same order as it is now customary to expect in structural determinations of organic substances; this may be attributed to the presence of the very heavy

strontium atom, which renders intensity measurements difficult; the contribution of the azide ion to the observed intensity is probably of the order of the experimental error for a high proportion of the planes.

Discussion of the Structure.—The equivalence of the two nitrogens at either end of the azide group—each is separated from the central nitrogen by 1.12 Å.—shows that the structure is ionic. Fig. 2 represents the disposition of the nearest azide ions around any strontium ion. The

FIG. 2.



strontium ion has eight near neighbours; these can conveniently be classified in two sets of four. In the first set the strontium–nitrogen separation is 2.63 Å., and in the second set 2.77 Å. Each azide ion is disposed between four strontium ions, two at a distance of 2.77 Å. and two at 2.63 Å.

Experimental. Strontium carbonate (5 g.) was dissolved in 2% hydrazoic acid (30 ml.) and the solution concentrated on a water-bath; on cooling, a mass of extremely small crystals was deposited. Larger crystals suitable for X-ray photography were obtained from the mother-liquor by slow evaporation in an Erlenmeyer flask.

This work forms part of a programme of fundamental research sponsored by the Ministry of Supply at the University of Birmingham; approval for publication has been granted by the Director General of Scientific Research and Development, Ministry of Supply.

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[Received, September 9th, 1946.]

165. The Crystal Structure of *p*-Dinitrobenzene.

By F. J. LLEWELLYN.

The crystal structure of *p*-dinitrobenzene has been completely determined by utilising all the diffracted beams obtainable with Cu- $K\alpha$ X-radiation. The molecule is centrosymmetrical, and the carbon atoms of the benzene nucleus are located on a regular hexagon such that the C–C distance is 1.38₈ Å. The nitro-group is planar, and coplanar with the rest of the molecule; its dimensions are C–N = 1.41, N–O = 1.23 Å.

THE crystal structure of *p*-dinitrobenzene has been previously investigated by Hertel (*Z. physikal. Chem.*, 1930, 7, B, 188), Bannerjee (*Phil. Mag.*, 1934, 18, 1004), and James, King, and Horrocks (*Proc. Roy. Soc.*, 1935, 153, A, 225); in the last investigation Mo- $K\alpha$ radiation was used to determine the intensities of the diffracted beams from the $\{h0l\}$, $\{hk0\}$, and $\{0kl\}$ planes—about 200 in all—the atomic parameters being determined by means of Fourier projections on the (a), (b), and (c) faces. The main features of the results are as follows: (i) The molecule of *p*-dinitrobenzene is centrosymmetrical; the benzene ring is not, however, a regular hexagon, as has previously been reported in other solid benzenoid substances, e.g., benzene (Cox, *Proc. Roy. Soc.*, 1932, 135, A, 491), hexamethylbenzene (Lonsdale, *ibid.*, 1929, 123, A, 494). (ii) The nitro-group and the carbon of the benzene ring to which it is bonded are not coplanar. (iii) The two oxygen atoms of the nitro-group are not equidistant from the nitrogen atom.

The irregularity of the benzene ring and the non-equivalence of the two oxygen atoms of the nitro-group are not compatible with the usual conceptions of the function of resonance

which is to be expected in such a substance; various objections to, and criticisms of, these results have been made (see Pauling, "Nature of the Chemical Bond," p. 201). It seemed probable that, whilst the general arrangement of the molecules in the unit cell had been correctly determined, the detailed description of the molecule was inaccurate, mainly because the number of intensities used in computing the Fourier synthesis was insufficient, and also because of the considerable overlapping which occurs in projecting the structure on to both the *a*- and the *c*-planes.

It was decided, therefore, to repeat the structure determination, utilising all the $\{hkl\}$ intensities obtainable with Cu-K α X-radiation—about 450 in all—and to ascertain the atomic co-ordinates by means of three-dimensional Fourier lines and sections.

Preliminary Crystallographic Data.—Small, well-defined, single crystals of *p*-dinitrobenzene were readily obtained by slow evaporation of an acetone solution; they exhibited the forms $\{110\}$, $\{100\}$, $\{101\}$, $\{011\}$, $\{111\}$; the symmetry appeared to be monoclinic holohedral and the habit was variable. X-Ray rotation and oscillation photographs confirmed the monoclinic symmetry and the axial dimensions previously reported by James *et al.* (*loc. cit.*), viz., $[a] = 11.05$ Å., $[b] = 5.42$ Å., $[c] = 5.65$ Å., $\beta = 92^\circ 18'$; whence $a : b : c = 2.039 : 1 : 0.42$. Axial ratios quoted by Bodewig (*Ann. Physik*, 1876, **158**, 239) are $a : b : c = 2.038 : 1 : 0.43$, $\beta = 92^\circ 18'$.

Various values for the density (g./c.c.) appear in the literature: 1.546 (Barker, *Z. Krist.*, 1908, **44**, 154), 1.625 (Lobry de Bruyn, *Rec. Trav. chim.*, 1894, **13**, 111), 1.623 (Brandl, quoted by Groth, "Chemische Kristallographie," **4**, 14), 1.64 (James *et al.*, *loc. cit.*); the density calculated from the X-ray data on the basis of two molecules in the unit cell is 1.64 (obs., by flotation, 1.63).

The only systematic halvings observed in the analysis of the X-ray oscillation photographs are $\{h0l\}$ absent when $h + l \neq 2n$, and $\{0k0\}$ absent when $k \neq 2n$. The space-group is therefore $P2_1/n(C_{2h}^2)$, which accommodates the four general positions $\pm(x, y, z)$ and $\pm(x + \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} + z)$ in each unit cell. Since there are only two molecules in the cell, it follows that these must be orientated about special two-fold positions, i.e., each molecule is centrosymmetrical.

Measurement of Intensities.—In order to make the structure determination as accurate as possible, the intensities of the diffracted beams from all the $\{hkl\}$ planes with spacings greater than 0.77 Å. were determined photographically. Since photographic density is proportional to X-ray intensity only over a limited range (from 0 to 1.2 approximately) it was necessary to take a number of oscillation photographs covering the same range of crystal orientation in order that all the diffracted beams which occur should be recorded as photographic spots whose density was within the proportionality limits. Two methods were adopted: (a) to vary the exposure, in which case the whole photograph was either more or less dense in proportion to this variation, or (b) to maintain the exposure constant but to screen (with aluminium sheets of known absorbing power) those parts of the photographic film on which the more intense diffracted beams fell such that their photographic impression lay within the proportionality limits.

The latter method was finally adopted, since it permitted an easy correlation between the strongest and weakest spots on a given photograph and considerably reduced the number of photographs necessary with (a) to achieve the same end. The actual measurement was carried out visually by matching each of the spots on the photographic film, in turn, with one of a series of spots of known density on a previously prepared comparator. The standard series of spots on the comparator was obtained as follows. A piece of X-ray film was exposed to a suitably collimated X-ray beam for a short measured time such that on development a photographic image was just discernible; a second piece of film was then exposed to the same X-ray beam for this time, then moved to a new position and exposed again for a longer time, this operation being repeated with successive increases in exposure until the necessary range of density was covered. The film was developed under conditions exactly similar to those obtaining in the photography of the crystal. In order to facilitate the matching of the spots, those on the comparator were made to approximate in both size and shape to those produced on the oscillation photographs.

A set of intensities on an arbitrary scale was thus produced, and these were converted to an absolute scale by direct photometric comparison of the intensities of the orders of (100) with the (400) reflection from the ground cleavage face of rock-salt. The experimental structure amplitudes ($F_{\text{obs.}}$) derived from the observed intensities Q by the relation

$$Q = \frac{N^2 e^4 \lambda^3}{2m^2 c^4} \cdot \frac{1 + \cos^2 2\theta}{\sin 2\theta} \cdot F^2$$

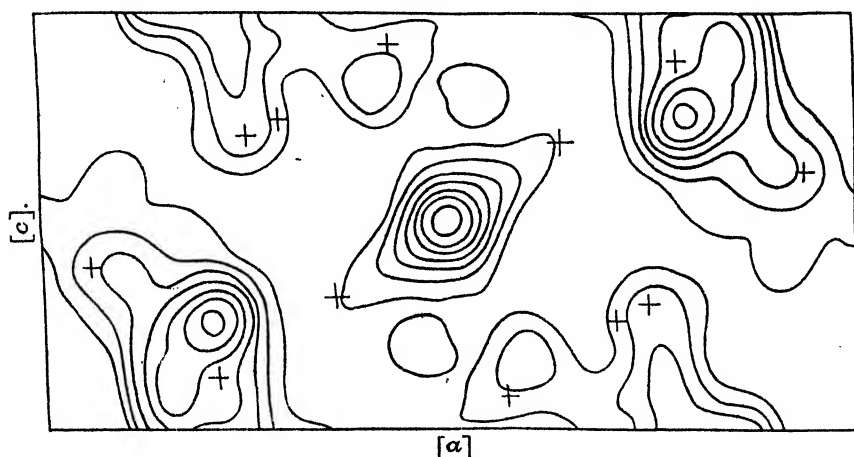
are listed in the table together with the calculated structure amplitudes ($F_{\text{calc.}}$) and the phase angles derived from the final atomic co-ordinates.

Determination of the Structure.—In order to define the structure it is necessary to determine the co-ordinates of six atoms, *viz.*, three carbons of the benzene ring, and one nitrogen and two oxygens of the nitro-group. The other half of the molecule is determinable by the operation of the centre of symmetry, and the second molecule by the operation of the glide plane. Since all the atoms in the structure are located in general positions, $\pm(x, y, z)$, $\pm(x + \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} + z)$, it is to be expected that a three-dimensional Harker-Patterson synthesis (*J. Chem. Physics*, 1936, 4, 381) evaluated at $y = \frac{1}{2}$ would exhibit maxima in the Patterson function P_{xzs} , where

$$P_{xzs} = \sum \sum \cos 2\pi(hx + lz) \left(\sum_k F_{hkl}^2 \cos 2\pi k/2 \right)$$

at the points $\pm(\frac{1}{2} - 2x_r, \frac{1}{2} - 2z_r)$, (x_r, z_r) being the co-ordinates of an atom, and thus provide for the direct determination of the (xz) co-ordinates of all the atoms in the structure. Such a three-dimensional synthesis was evaluated, and the resulting contour map (Fig. 1) plotted over the whole unit cell; it is obvious that the maxima are too diffuse to be of any great service in determining accurate atomic co-ordinates.

FIG. 1.

Patterson-Harker Section at $y = \frac{1}{2}$.

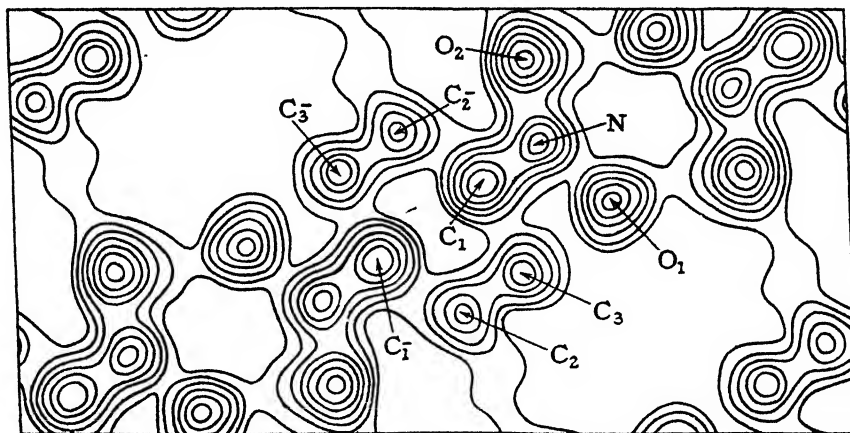
This result is in sharp contrast with that obtained in the determination of the structure of pentaerythritol (Llewellyn, Cox, and Goodwin, *J.*, 1937, 883) in which a Patterson-Harker three-dimensional summation gave rise to sharp maxima in the function P_{xy0} and permitted the accurate determination of the (xy) co-ordinates of the pentaerythritol molecule. It is interesting to compare the positions of the maxima P_{xzs} as represented by the peaks in Fig. 1 with the positions (represented by crosses) of the maxima calculated from the final atomic co-ordinates. Although it may be allowed that there is qualitative coincidence, yet the value of the Patterson synthesis in determining even approximate atomic co-ordinates is practically negligible. This question is further discussed by Booth and Llewellyn (this vol., p. 839).

It became necessary therefore to postulate a molecule and a molecular orientation and to refine the resulting atomic co-ordinates in three stages: (i) by trial-and-error methods using the $\{h0l\}$ structure amplitudes to determine the x and z co-ordinates; (ii) to refine these co-ordinates by two-dimensional Fourier syntheses; (iii) to obtain approximate y co-ordinates from a consideration of the x and z co-ordinates determined in (ii) and the bond lengths postulated in the molecule, and to refine these (xyz) co-ordinates by three-dimensional Fourier sections and lines.

The model used in the first stages consisted of a regular hexagon for the benzene ring with carbon-carbon separations of 1.39 Å., a planar $\text{R}\cdot\text{NO}_2$ group which was coplanar with the benzene ring with carbon-nitrogen separation of 1.47 Å., and a nitrogen-oxygen separation of 1.23 Å. This model was placed in the unit cell with the centre of the benzene ring coincident with the centre of symmetry (origin) and orientated by trial-and-error methods until approx-

imate agreement between the observed and calculated values of a few $\{h0l\}$ structure amplitudes was obtained. The (xz) co-ordinates were then refined by means of a number of two-dimensional Fourier projections involving all the $\{h0l\}$ amplitudes. The resulting contour map is shown in Fig. 2.

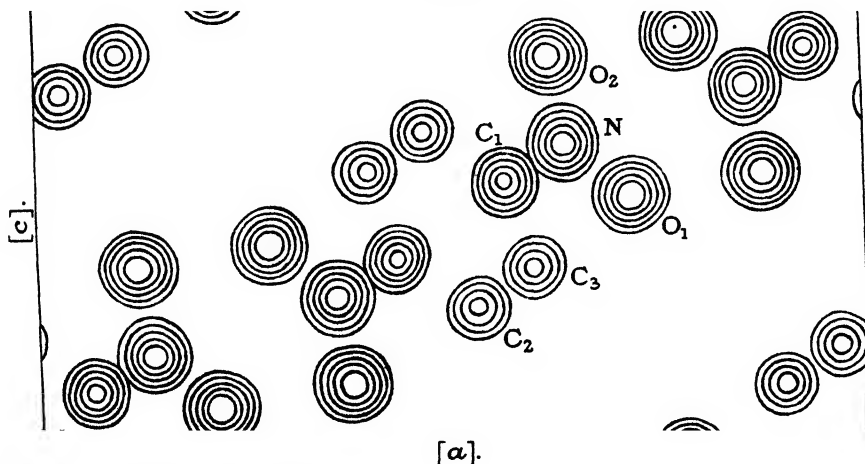
FIG. 2.



Fourier Projection on to 010.

These co-ordinates were then used in conjunction with the model to calculate approximate y co-ordinates. With these (xyz) co-ordinates the phase angles of all the $\{hkl\}$ structure amplitudes were calculated, and then the co-ordinates refined by successive three-dimensional Fourier lines parallel to $[010]$ at the xy co-ordinates of each atom in turn and by three-dimensional Fourier sections parallel to (010) at the y co-ordinates of each of the atoms. After two such complete cycles of operations the agreement between the calculated and the observed structure amplitudes became satisfactory; a third set of syntheses resulted in no alteration of the phase angles. The various Fourier sections are illustrated in a composite drawing in Fig. 3.

FIG. 3.



The final atomic co-ordinates are :

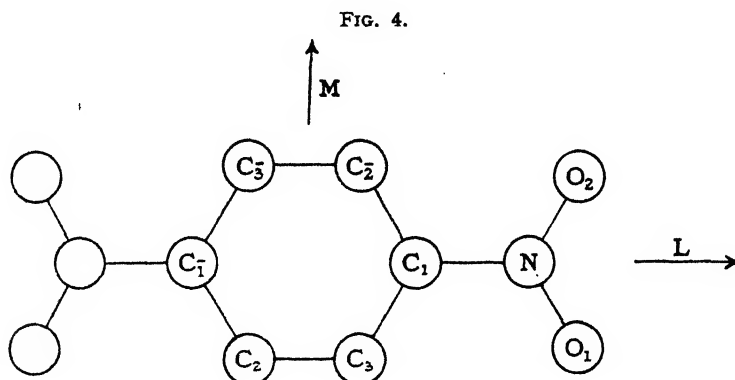
Atom.	x .	y .	z .	Atom.	x .	y .	z .
C ₁	0.070	0.192	0.090	N	0.142	0.387	0.184
C ₂	0.032	-0.117	-0.206	O ₁	0.220	0.472	0.057
C ₃	0.102	0.075	-0.115	O ₂	0.124	0.460	0.385

The average discrepancy between observed and calculated structure factors is 24%.

h.	0.		1.		2.		3.		4.		5.	
	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}
00	172.0	—	—	—	25.1	+27.2	—	—	4.1	-3.0	—	—
01	—	—	7.6	+8.2	8.5	+9.0	7.8	-6.0	9.6	+11.5	<1.2	0.5
02	2.5	+1.6	9.6	-10.6	3.9	+7.8	4.1	+3.0	7.7	+9.8	5.4	5.0
03	—	—	12.3	-10.1	7.2	7.4	4.9	-4.5	9.9	10.4	1.4	-1.7
04	14.0	-12.2	1.9	3.1	3.4	-4.5	5.6	6.6	<1.1	-2.0	<0.9	-2.7
05	—	—	4.1	-6.1	2.5	-3.1	<1.1	0.5	<1.0	0.3	—	—
06	2.8	-3.0	2.9	-4.6	<1.0	-1.5	—	—	—	—	—	—
10	—	—	1.9	-0.4	14.0	+12.5	15.6	-13.2	8.8	8.5	1.0	-0.5
11	1.7	0.8	23.8	-30.4	12.9	-13.6	12.4	-10.9	5.2	-4.5	1.5	0.8
12	—	—	7.2	6.8	4.5	-3.6	3.4	-0.5	7.6	6.8	1.7	-2.6
13	22.9	-22.0	1.7	2.8	4.9	-4.7	6.0	+6.4	2.6	1.0	1.4	-4.0
14	—	—	1.9	3.7	4.7	0	7.3	8.0	<1.2	+0.6	1.6	+2.7
15	<1.2	0.6	4.2	-1.0	2.8	0.9	1.6	-1.4	2.1	4.0	—	—
16	—	—	4.7	3.4	2.3	0.4	—	—	—	—	—	—
20	9.3	7.2	25.8	-28.6	17.8	-16.4	18.6	-16.1	7.7	-7.0	3.3	-5.2
21	—	—	38.3	52.0	16.3	-19.6	6.8	4.4	1.1	-1.5	2.9	-2.9
22	7.3	-4.4	6.2	-5.6	5.3	6.0	4.6	5.3	2.1	3.4	1.8	1.7
23	—	—	6.4	7.5	3.2	-1.9	12.4	13.2	2.9	2.7	1.1	2.0
24	1.6	-1.0	6.2	6.4	1.5	3.5	8.3	9.5	3.9	-2.0	3.1	4.7
25	—	—	3.3	-2.4	5.7	5.7	<1.1	-0.7	<1.0	1.4	—	—
26	4.3	-6.0	<1.1	0.5	1.1	-1.9	—	—	—	—	—	—
30	—	—	35.6	32.4	3.8	-2.4	<1.0	-0.5	1.4	0.9	1.5	-0.5
31	5.3	-2.4	9.6	-8.2	1.5	3.2	7.6	6.7	1.6	+0.2	4.5	5.4
32	—	—	10.9	-8.4	15.5	-13.6	1.8	2.7	<1.2	-0.1	2.9	-2.4
33	1.4	-3.0	3.8	3.0	4.8	4.4	5.2	5.8	1.6	-2.0	2.7	1.6
34	—	—	10.0	-9.9	9.3	6.6	<1.2	1.7	<1.1	-0.7	—	—
35	<1.2	1.9	1.8	0.9	2.6	2.9	<1.1	1.1	—	—	—	—
36	—	—	<1.0	-0.5	<0.9	-0.9	—	—	—	—	—	—
40	23.9	-18.0	1.7	-2.4	7.3	-5.9	8.3	7.1	2.5	2.4	<1.0	-0.1
41	—	—	18.0	-20.0	21.5	-25.4	8.0	-9.5	4.3	-5.3	4.7	-5.6
42	12.3	14.0	10.7	-9.2	11.8	13.0	9.8	-8.4	<1.2	0.3	2.3	-3.3
43	—	—	6.8	-7.5	<1.1	1.4	6.8	6.2	1.7	-1.7	<1.0	-0.8
44	5.2	9.4	2.5	1.7	8.3	11.0	<1.2	2.6	2.2	3.7	—	—
45	—	—	5.3	6.9	5.3	4.4	<1.2	-1.0	—	—	—	—
46	2.0	3.0	2.1	3.1	—	—	—	—	—	—	—	—
50	—	—	5.2	-4.4	7.0	-6.6	2.6	-2.4	2.9	1.3	2.3	-1.8
51	21.3	20.6	6.0	-5.7	15.9	13.2	4.0	-3.7	1.0	-1.5	2.2	-3.9
52	—	—	6.9	-3.2	2.7	-1.8	8.8	8.8	<1.2	1.8	<1.1	2.5
53	8.5	-5.4	2.7	-2.5	2.2	3.3	6.6	-6.5	<1.2	2.1	<1.0	-0.7
54	—	—	4.1	5.5	8.2	7.1	<1.2	0.8	<1.0	1.1	—	—
55	1.2	-3.0	2.1	5.0	1.6	-4.3	<1.0	1.9	—	—	—	—
56	—	—	2.0	2.2	—	—	—	—	—	—	—	—
60	10.5	-8.2	9.4	7.1	1.7	-1.2	11.7	10.9	3.4	-3.7	<1.0	-0.1
61	—	—	10.9	-7.2	5.7	3.7	3.7	4.0	3.8	4.4	1.1	2.8
62	24.0	-20.0	7.9	-6.8	8.9	-9.6	8.7	-9.0	2.1	-4.0	<1.0	0.3
63	—	—	<1.2	-0.4	<1.2	-0.4	1.2	2.3	<1.2	-0.4	—	—
64	6.8	-8.4	4.1	4.3	1.9	-3.5	1.2	-2.0	<1.0	0.3	—	—
65	—	—	5.3	6.6	1.1	-2.6	—	—	—	—	—	—
70	—	—	6.9	-5.0	4.2	4.8	7.4	5.9	1.0	0.1	1.1	1.2
71	6.2	-6.4	<1.2	-1.4	2.3	-3.1	2.4	-3.0	3.5	-5.0	<1.0	0.6
72	—	—	6.7	4.1	2.4	-2.8	3.7	3.1	5.0	-5.6	—	—
73	8.1	-5.6	2.8	2.4	<1.2	1.6	<1.1	-1.6	—	—	—	—
74	—	—	<1.2	0	1.7	-1.8	<1.1	1.4	—	—	—	—
75	7.5	8.0	2.7	3.4	<1.0	2.3	—	—	—	—	—	—
80	7.2	7.8	5.2	4.1	9.2	10.2	3.5	4.0	1.0	-0.3	—	—
81	—	—	3.6	4.0	10.1	8.1	<1.2	-0.5	<1.0	0.7	—	—
82	4.8	-1.6	4.2	3.0	<1.2	2.6	<1.2	2.0	1.9	5.5	—	—
83	—	—	7.8	-7.2	<1.2	-1.7	<1.0	-3.6	—	—	—	—
84	<1.0	0.2	2.4	3.0	1.9	-1.1	<1.0	0.7	—	—	—	—
85	—	—	1.3	-4.6	—	—	—	—	—	—	—	—
90	—	—	6.5	-4.7	10.5	11.1	<1.2	-2.4	1.7	2.1	—	—
91	1.8	-1.0	5.6	4.5	<1.2	1.1	<1.2	0.7	1.0	0.5	—	—
92	—	—	2.1	-4.0	<1.2	-0.9	3.4	-6.2	1.2	-0.5	—	—
93	<1.0	1.3	1.4	1.3	<1.2	-0.5	<1.0	0	—	—	—	—
94	—	—	2.5	-3.1	<1.0	1.7	—	—	—	—	—	—
10.0	1.7	-0.8	1.8	1.3	3.1	2.4	3.3	-4.5	—	—	—	—
10.1	—	—	8.5	8.0	2.7	1.8	<1.0	-0.3	—	—	—	—
10.2	7.7	7.0	3.9	1.6	<1.2	0.8	<1.0	0.2	—	—	—	—
10.3	—	—	1.8	0.2	<1.0	1.4	—	—	—	—	—	—
10.4	<1.0	2.0	—	—	—	—	—	—	—	—	—	—

h	0.		1.		2.		3.		4.		5.	
h	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}	F _{obs.}	F _{calc.}
11·0	—	—	6·1	7·5	1·9	3·0	0·7	3·9	—	—	—	—
11·1	3·1	1·9	6·2	5·4	1·1	-1·6	1·0	0·5	—	—	—	—
11·2	—	—	2·2	3·1	<1·0	0	—	—	—	—	—	—
11·3	1·5	-0·9	<1·0	-0·9	—	—	—	—	—	—	—	—
12·0	3·4	-5·8	3·6	4·3	2·6	-4·0	—	—	—	—	—	—
12·1	—	—	<1·0	3·1	—	—	—	—	—	—	—	—
12·2	7·2	8·1	—	—	—	—	—	—	—	—	—	—
1I	32·7	-48·8	9·6	11·8	5·1	1·6	1·3	1·5	2·3	-2·4	3·8	-3·1
12	—	—	13·5	-10·6	0·7	-2·4	3·1	-1·0	1·3	-1·5	5·2	4·2
13	5·9	3·0	8·2	2·9	9·1	8·8	<1·1	-4·0	5·5	10·8	<1·0	-0·8
14	—	—	3·1	-0·4	2·9	2·4	2·9	-4·1	<1·0	-2·5	2·6	-2·8
15	3·6	5·0	1·4	+0·2	1·9	5·1	1·3	1·3	1·3	+2·0	—	—
16	—	—	2·7	-6·6	2·4	2·3	—	—	—	—	—	—
2I	—	—	12·8	-9·0	6·0	5·2	1·1	-1·9	1·4	-2·6	7·8	6·9
22	21·0	-19·6	2·0	0·4	20·4	-20·0	4·1	-3·8	3·0	-2·8	5·1	-4·2
23	—	—	12·0	-11·1	3·8	-3·0	5·7	-5·1	<1·2	0·9	3·1	2·4
24	3·2	-4·0	5·4	5·4	4·4	-3·7	<1·2	0·9	<1·1	1·5	<1·0	1·4
25	—	—	4·0	2·8	9·5	11·4	<1·1	-1·6	1·8	4·1	—	—
26	2·5	6·0	3·8	2·0	3·2	7·2	—	—	—	—	—	—
3I	5·2	4·4	7·2	-8·6	8·2	-5·0	1·6	1·1	<3·2	2·5	1·4	0·9
32	—	—	4·9	2·6	<1·0	-0·2	9·5	10·6	<3·2	-1·9	11·1	10·8
33	1·5	-0·8	3·1	1·4	10·1	-6·5	<1·2	-1·0	4·1	-3·0	1·1	-1·3
34	—	—	7·7	8·2	2·5	-1·3	3·2	-2·5	1·9	-1·6	—	—
35	1·7	-5·2	4·3	4·3	1·9	-3·9	<1·1	-0·3	—	—	—	—
36	—	—	2·4	-0·5	3·6	6·4	—	—	—	—	—	—
4I	—	—	19·8	-17·9	7·9	8·9	9·6	-9·6	5·6	4·4	1·1	0
42	4·0	-3·6	6·4	-2·8	8·2	-6·0	5·9	6·8	2·0	3·7	5·9	8·3
43	—	—	5·4	2·9	<1·1	-0·8	2·9	3·1	2·1	1·4	4·9	5·7
44	13·8	15·6	6·5	6·4	1·5	1·2	1·2	5·3	3·1	-2·7	—	—
45	—	—	9·4	11·6	1·9	1·0	<1·1	1·8	—	—	—	—
46	2·5	-3·1	1·7	3·4	—	—	—	—	—	—	—	—
5I	9·6	-8·8	6·2	-2·4	5·8	3·8	3·9	5·0	8·9	9·7	1·4	-2·6
52	—	—	15·4	14·8	1·2	1·2	8·8	-10·5	4·8	3·5	<1·0	-1·8
53	12·5	10·6	9·8	-5·9	<1·1	-1·0	1·2	-0·9	<1·2	-1·9	<1·0	4·6
54	—	—	1·2	-3·5	<1·2	-0·4	<1·2	-2·2	<1·1	-0·3	—	—
55	7·3	7·0	5·1	6·0	<1·8	0·1	<1·1	1·8	—	—	—	—
56	—	—	1·0	2·6	—	—	—	—	—	—	—	—
6I	—	—	3·2	5·0	2·3	4·8	3·6	5·8	7·7	9·7	<1·1	-1·5
62	3·1	1·8	7·8	-7·0	8·5	7·2	<1·2	0·4	7·6	7·1	1·8	1·4
63	—	—	8·6	8·2	<1·2	-0·2	<1·2	-1·8	<1·2	3·5	—	—
64	18·3	18·7	5·4	-4·3	2·7	3·1	1·2	-5·0	<1·0	-2·1	—	—
65	—	—	2·1	-4·0	<1·1	-4·1	—	—	—	—	—	—
7I	21·5	-19·2	4·6	5·2	6·9	-7·0	7·6	8·9	1·8	-3·7	1·0	2·5
72	—	—	5·2	5·2	8·2	-4·5	2·0	2·4	2·4	5·0	1·1	-1·3
73	<1·2	-1·6	7·1	-7·2	1·2	-3·0	<1·2	-1·6	<1·1	0·7	—	—
74	—	—	7·9	7·1	1·2	3·0	<1·1	-0·4	—	—	—	—
75	4·4	7·8	<1·2	-1·4	1·0	1·5	—	—	—	—	—	—
8I	—	—	1·0	1·5	2·7	-3·0	8·4	10·0	1·2	-2·2	—	—
82	1·9	-2·2	2·4	-2·7	2·3	2·0	<1·2	0·4	<1·2	-0·5	—	—
83	—	—	6·8	6·1	10·3	-9·0	<1·2	-1·2	<1·1	-3·1	—	—
84	3·7	-5·7	4·0	-3·5	4·9	-6·7	<1·1	-1·6	—	—	—	—
85	—	—	<1·0	-0·9	—	—	—	—	—	—	—	—
9I	3·1	4·0	<1·2	0·6	7·0	10·0	1·1	1·8	<1·1	1·4	—	—
92	—	—	2·3	-2·8	6·3	-6·1	4·4	4·1	<1·0	-0·7	—	—
93	3·9	5·1	4·4	-1·7	3·7	5·4	1·1	1·4	—	—	—	—
94	—	—	1·8	4·9	2·3	-3·3	—	—	—	—	—	—
10I	—	—	5·1	-5·9	1·8	2·2	1·4	0·9	—	—	—	—
102	<1·1	-0·3	4·4	-2·9	1·9	1·9	5·6	-4·8	—	—	—	—
103	—	—	1·7	-6·6	3·1	-4·1	1·0	-2·5	—	—	—	—
104	1·9	-0·2	—	—	—	—	—	—	—	—	—	—
11I	5·2	-3·6	1·2	-1·6	1·2	1·8	3·7	-5·4	—	—	—	—
112	—	—	2·0	1·1	<1·2	0·8	—	—	—	—	—	—
113	1·0	1·3	1·0	-2·8	—	—	—	—	—	—	—	—
12I	—	—	1·3	-0·1	1·2	1·1	—	—	—	—	—	—
122	4·9	-6·4	<1·0	1·1	—	—	—	—	—	—	—	—

Description of the Structure.—A diagrammatic representation of the *p*-dinitrobenzene molecule is shown in Fig. 4. The atoms C_1, C_2 , etc., are obtained by inversion of the atoms C_1, C_2 , etc., across the centre of symmetry coincident with the centre of the molecule. Within the limits of experimental error all the atoms lie in a plane which is so orientated within the



unit cell that the molecular axes, L and M , make angles of $48^\circ 42'$ and $5^\circ 42'$ respectively with the plane 010. Bond angles and bond lengths calculated from the measured atomic co-ordinates and cell dimensions are as follows:

$C_1-C_2 = 1.38_5 \text{ \AA.}$	$C_1-N = 1.41 \text{ \AA.}$	$\angle O_1-N-O_2 = 124^\circ$
$C_2-C_3 = 1.38_5 \text{ \AA.}$	$N-O_1 = 1.23 \text{ \AA.}$	$\angle O_1-N-C_1 = 117_4^\circ$
$C_3-C_4 = 1.38_5 \text{ \AA.}$	$N-O_2 = 1.23 \text{ \AA.}$	$\angle O_2-N-C_1 = 118_4^\circ$

Other distances within the molecule are: $O_1-O_2 = 2.17$; $C_1-O_1 = 2.25$; $C_1-O_2 = 2.25 \text{ \AA.}$ The error in the bond lengths is probably not more than $\pm 0.02 \text{ \AA.}$, and the angles are probably accurate to within $\pm 2^\circ$.

The anomalies in the bond lengths and bond angles reported by James (*loc. cit.*) are not substantiated by the present investigation. The benzene ring is a regular hexagon, and in this respect falls into line with the results of earlier structural work on benzenoid substances.

The two oxygen atoms of the nitro-group are equidistant at 1.23 \AA. from the nitrogen atom. This result is in agreement with the resonance mechanism suggested by Pauling in which the two principal forms are:



The observed distance, 1.23 \AA. , is greater than the calculated value of 1.19 \AA. and agrees more nearly with the value of 1.21 ± 0.02 found in nitromethane. The ONO bond angle is 124° as compared with 127° found in nitromethane and the theoretical value of $125^\circ 16'$.

This work forms part of a programme of fundamental research sponsored by the Ministry of Supply at the University of Birmingham; approval for publication has been granted by the Director General of Scientific Research and Development, Ministry of Supply.

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[Received, September 9th, 1946.]

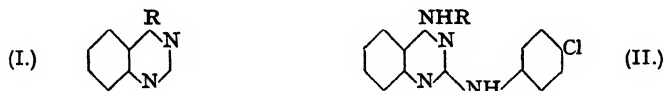
166. Synthetic Antimalarials. Part XVI. 4-Dialkylaminoalkylamino-quinazolines. Variation of Substituents in the 6- and 7-Positions.

By NORMAN B. CHAPMAN, GEOFFREY M. GIBSON, and FREDERICK G. MANN.

A series of seven quinazolines having different dialkylaminoalkylamino-groups in the 4-position has been prepared. Series of 4-dialkylaminoalkylaminoquinazolines, having in addition the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents, have also been synthesised. This wide range of quinazolines has been tested for antimalarial activity and some noteworthy variations have been revealed.

THIS investigation originated in the observation made in the laboratories of Imperial Chemical Industries Ltd. that 4- γ -diethylaminopropylaminoquinazoline (I; $R = \text{NH} \cdot [\text{CH}_2]_3 \cdot \text{NEt}_2$) showed activity against *P. gallinaceum* in chicks. This result was apparently at variance with those of Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, 8, 1797) who first prepared this compound, its 6-chloro-derivative, and several other 6-substituted 4-dialkylaminoalkylaminoquinazolines and reported that they possessed no antimalarial activity. It appeared that the apparent discrepancy might possibly be due to a species specificity which these quinazoline derivatives might show in their antimalarial action, the Russian workers having probably tested the compounds against *P. præcox* (cf. Magidson *et al.*, *J. Microbiol. and Immunobiol.*, 1934, 13, 685; *Trop. Dis. Bull.*, 1935, 32, 419).

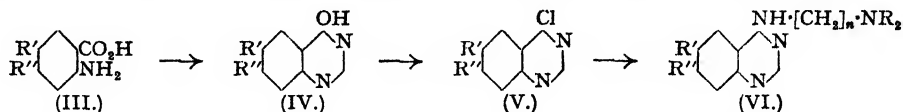
In view of the fact that 2-*p*-chloroanilino-4-dialkylaminoalkylaminoquinazolines of type (II; $R = \text{dialkylaminoalkyl}$) had also been shown to possess marked antimalarial activity against *P. gallinaceum* in chicks (Curd, Landquist, and Rose, Part XIV, this vol., p. 775) it became desirable to make a systematic study of the relationship between structure and antimalarial activity in 4-dialkylaminoalkylaminoquinazolines of type (I). Accordingly, we first prepared a series of compounds of type (I) having no substituent in the benzene ring, but



having in turn seven different dialkylaminoalkylamino-groups in the 4-position. We then prepared five similar series of compounds having in turn the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents. Our choice both of these groups and their position was determined largely by the presence of the same groups in analogous positions in various quinoline and acridine compounds of known antimalarial activity. Thus, for instance, Magidson and Rubtsov (*J. Gen. Chem. Russia*, 1937, 7, 1896) and Schönhöfer (*Z. physiol. Chem.*, 1942, 274, 1) have reported on the antimalarial activity of 4-dialkylaminoalkylamino-6-methoxyquinolines, and D.R.-P. 683,692 relates *inter alia* to 7-halogeno-4-dialkylaminoalkylaminoquinolines which are stated to possess antimalarial activity. 7-Nitro-4- β -diethylaminoethylamino-3-ethoxyacridine (Magidson and Grigorowsky, *Ber.*, 1936, 69, 396) is an example of an active antimalarial containing a nitro-group.

Over forty 4-dialkylaminoalkylaminoquinazolines have thus been prepared. In addition, some of the 4-hydroxyquinazoline derivatives utilised as intermediates in the synthesis of these quinazolines (*vide infra*) have also been submitted for test for prophylactic action because they were seen to be distantly related to Endochin (4-hydroxy-7-methoxy-3-*n*-heptylquinaldine) (C.I.O.S. Reports Nos. XXIII, 12, 13; XXIV, 20; XXV, 54, H.M. Stationery Office; see also Fitch, *Pharm. J.*, 1945, 182) which is stated to possess prophylactic activity against avian malaria.

The general route employed for the preparation of all these quinazolines consisted first in heating the appropriate anthranilic acid (or ester) (III) with formamide to obtain the



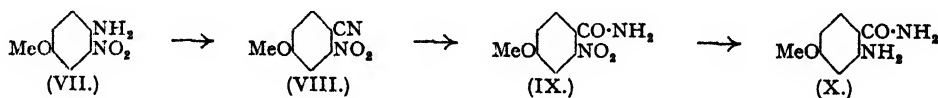
corresponding 4-hydroxyquinazoline (IV), which when suitably treated with a mixture of phosphorus pentachloride and phosphorus oxychloride gave the 4-chloroquinazoline (V). This when boiled in alcoholic solution with the dialkylaminoalkylamine furnished the 4-dialkylaminoalkylaminoquinazoline (VI), which was isolated either as the free base or directly as the hydrochloride.

The various substituted anthranilic acids and quinazoline intermediates were prepared as follows. Direct chlorination of methyl anthranilate (Freundler, *Bull. Soc. chim.*, 1911, 9, 606) gave methyl 5-chloroanthranilate (as III; $R' = \text{Cl}$, $R'' = \text{H}$) which readily condensed with formamide to give 6-chloro-4-hydroxyquinazoline (IV; $R' = \text{Cl}$, $R'' = \text{H}$) and thence 4:6-dichloroquinazoline (V; $R' = \text{Cl}$, $R'' = \text{H}$) (cf. Magidson *et al.*, *loc. cit.*). 4-Chloroanthranilic acid (III; $R' = \text{H}$, $R'' = \text{Cl}$) was prepared by a modification (Curd *et al.*, forthcoming communication) of Cohn's method (*Monatsh.*, 1901, 22, 485), 4-chloroaceto-*o*-toluidide being oxidised to 4-chloroacetylthranilic acid, and then hydrolysed in turn to

4-chloroanthranilic acid. This acid furnished 7-chloro-4-hydroxyquinazoline (IV; $R' = H$, $R'' = Cl$) and 4:7-dichloroquinazoline (V; $R' = H$, $R'' = Cl$). 4-Nitroanthranilic acid (III; $R' = H$, $R'' = NO_2$), similarly prepared from 4-nitroaceto-*o*-toluidide, furnished 7-nitro-4-hydroxy- and 4-chloro-7-nitro-quinazolines (IV and V; $R' = H$, $R'' = NO_2$).

5-Methoxyanthranilic acid (III; $R' = OMe$, $R'' = H$) was prepared by oxidising 2-nitro-5-methoxybenzaldehyde (Mason, *J.*, 1925, 1195) to 2-nitro-5-methoxybenzoic acid and reducing the latter. This acid gave 4-hydroxy-6-methoxy- and 4-chloro-6-methoxy-quinazoline (IV and V; $R' = OMe$, $R'' = H$).

4-Methoxyanthranilamide (X) was prepared by converting 2-nitro-4-methoxyaniline (VII) into 2-nitro-4-methoxyphenyl cyanide (VIII) (cf., Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 861), which on short treatment with sulphuric acid yielded 2-nitro-4-methoxybenzamide



(IX); reduction with ferrous hydroxide then gave (X). 4-Hydroxy-7-methoxyquinazoline (IV; $R' = H$, $R'' = OMe$) was readily prepared by the action of formic acid on this amide; it was also prepared, but less effectively, by the action of formamide on 4-methoxyanthranilic acid or its methyl ester. The usual treatment then furnished 4-chloro-7-methoxyquinazoline (V; $R' = H$, $R'' = OMe$).



In addition to the above quinazolines in which substituents in the pyrimidine ring were limited to the 4-position, the preparation of 2-amino-4-dialkylaminoalkylaminoquinazolines has been investigated, since Hull, Lovell, Openshaw, Payman, and Todd (Part III, *J.*, 1946, 357) have reported that the corresponding 2-amino-4-dialkylaminoalkylamino-5:6-dimethylpyrimidines possessed antiparasitic activity. For this purpose 2-chloro-4- β -diethylaminoethylaminoquinazoline (XI; $R = NH \cdot [CH_2]_2 \cdot NEt_2$) was heated with alcoholic ammonia to give 2-amino-4- β -diethylaminoethylaminoquinazoline (XII; $R = NH \cdot [CH_2]_2 \cdot NEt_2$), but the yield, which was never high, was markedly decreased by even small changes in the time and temperature of heating. 2-Chloro-4- β -diethylaminoethylaminoquinazoline (cf. Part XIV, *loc. cit.*) was very conveniently prepared by boiling 2:4-dichloroquinazoline (Lange, Roush, and Asbeck, *J. Amer. Chem. Soc.*, 1930, 52, 3698) in alcoholic solution with one equivalent of β -diethylaminoethylamine. 2-Chloro-4- δ -diethylamino- α -methylbutylaminoquinazoline (XI; $R = NH \cdot CHMe \cdot [CH_2]_3 \cdot NEt_2$) was similarly prepared, but this compound could not be satisfactorily converted into the 2-amino-derivative by the action of either alcoholic ammonia or potassium phthalimide. Many attempts were also made to convert 2-chloro-4-methylthioquinazoline (XI; $R = SMe$) (Part XIV) and 2-chloro-4-phenoxyquinazoline (Lange *et al.*, *loc. cit.*) by the action of alcoholic ammonia into their 2-amino-derivatives, in the expectation that the 4-substituent might then be replaced by the δ -diethylamino- α -methylbutylamino-group, but conditions sufficiently vigorous to replace the 2-chlorine atom by the amino-group appeared always to replace similarly the 4-substituent.

Attempts to prepare the 2-amino-compound from 2-chloro-4- β -diethylaminoethylamino-7-methoxyquinazoline also failed. This compound, although first prepared in the laboratories of Imperial Chemical Industries Ltd., has not yet been reported and is therefore described in this paper. Its synthesis involved the preparation of 2:4-dihydroxy-7-methoxyquinazoline from 2-carbamido-4-methoxybenzoic acid, followed by conversion into 2:4-dichloro-7-methoxyquinazoline and condensation with β -diethylaminoethylamine.

The antimalarial activity (against the blood invasive forms of *P. gallinaceum*) of all the above 4-dialkylaminoalkylaminoquinazolines has been estimated by tests in chicks, by the method described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, 39, 139). The results are summarised in Table I where the usual method of expressing antimalarial activity is employed. For the antimalarial tests, certain of the 4-substituted quinazolines were weighed as free base (anhydrous or hydrated) which was then solubilised with dilute lactic acid: others were weighed as hydrochlorides or sulphates. The particular compound (base or salt) is accordingly indicated in column 4.

TABLE I.
Antimalarial Activity of 4-Substituted Quinazolines.
Substituent:

Ref. No.	6- or 7-position.	4-position.	Weighed as	Dose, mg./kg.	Activity.
5022	—	NH·[CH ₂] ₃ ·NEt ₂	base	40	—
5023	—	NH·[CH ₂] ₃ ·NMe ₂	"	80	++
				60	+
				40	—
3623 *	—	NH·[CH ₂] ₃ ·NEt ₂	"	120	++
				40	—
5064	—	NH·[CH ₂] ₃ ·NHBu ^a	"	160	±
				80	—
5024	—	NH·[CH ₂] ₃ ·NBu ^a ₂	"	40	—
5021	—	NH·CHMe·[CH ₂] ₃ ·NEt ₂	"	60	++
				40	+
5026	—	NH·[CH ₂] ₃ ·O·[CH ₂] ₂ ·NEt ₂	"	80	—
5025	—	NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	monohydrate	80	—
5683	6-Cl	OH	base	20	—
5684	"	NH·[CH ₂] ₂ ·NEt ₂	monohydrochloride	160	—
				80	—
				40	—
5688	"	NH·[CH ₂] ₃ ·NMe ₂	"	160	+
				80	±
5685	"	NH·[CH ₂] ₃ ·NEt ₂	"	160	±
				80	—
5689	"	NH·[CH ₂] ₃ ·NBu ^a ₂	"	160	—
5687	"	NH·CHMe·[CH ₂] ₃ ·NEt ₂	base	80	+ to ++
				40	—
5686	"	NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	monohydrochloride	160	—
5245	7-Cl	NH·[CH ₂] ₄ ·NEt ₂	base	80	+ to ++
				40	—
5248	"	NH·[CH ₂] ₃ ·NMe ₂	"	80	++
				40	+ to ++
				20	—
5247	"	NH·[CH ₂] ₃ ·NEt ₂	"	80	++
				40	+
				20	±
5249	"	NH·[CH ₂] ₃ ·NBu ^a ₂	"	160	++
				80	+
				40	—
5246	"	NH·CHMe·[CH ₂] ₃ ·NEt ₂	"	20	++
				10	—
5251	"	NH·[CH ₂] ₃ ·O·[CH ₂] ₂ ·NEt ₂	"	80	++
				40	+
				20	±
5250	"	NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	hemihydrate	160	++
				80	+
5682	7-NO ₂	OH	base	not tested	
5407	"	NH·[CH ₂] ₃ ·NEt ₂	monohydrochloride	320	+ to ++
				160	—
5409	"	NH·[CH ₂] ₃ ·NMe ₂	"	160	—
5408	"	NH·[CH ₂] ₃ ·NEt ₂	"	160	—
5410	"	NH·[CH ₂] ₃ ·NBu ^a ₂	"	160	±
				80	—
5406	"	NH·CHMe·[CH ₂] ₃ ·NEt ₂	"	320	++
				160	+ to ++
				80	—
5412	"	NH·[CH ₂] ₃ ·O·[CH ₂] ₂ ·NEt ₂	"	160	—
5411	"	NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	"	160	—
6123	6-OMe	OH	base	80	—
6117	"	NH·[CH ₂] ₃ ·NEt ₂	disulphate	140	—
6121	"	NH·[CH ₂] ₃ ·NMe ₂	base	80	+ to ++
6118	"	NH·[CH ₂] ₃ ·NEt ₂	disulphate	140	+
6122	"	NH·[CH ₂] ₃ ·NBu ^a ₂	"	120	—
6120	"	NH·CHMe·[CH ₂] ₃ ·NEt ₂	monohydrate	80	++
6119	"	NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	base	80	+
5681	7-OMe	OH	"	not tested	
5252	"	NH·[CH ₂] ₃ ·NEt ₂	"	160	++
				80	+

* Prepared by Dr. J. K. Landquist, Imperial Chemical Industries Ltd. (Dyestuffs Division).

TABLE I—*contd.*

Ref. No.	Substituent:		Weighed as	Dose, mg./kg.	Activity.
	6- or 7-position.	4-position.			
5256	7-OMe	NH·[CH ₂] ₃ ·NMe ₂	base	80 40	++ —
5253	..	NH·[CH ₂] ₃ ·NEt ₃	disulphate	160 80	+ to ++ —
5257	..	NH·[CH ₂] ₃ ·NBu ₃	..	160 80	+ —
5255	..	NH·CHMe·[CH ₂] ₃ ·NEt ₂	base	40 20	++ +
5258	..	NH·[CH ₂] ₃ ·O·[CH ₂] ₂ ·NEt ₂	monohydrate	160 80	++ ±
5254	..	NH·[CH ₂] ₃ ·N<[CH ₂] ₄ >CH ₂	base	80 40	++ +
5622	2-amino-4-β-diethylaminoethylamino-quinazoline		..	40 20	++ +

The following 4-hydroxyquinazolines were tested for prophylactic activity against *P. gallinaceum* in chicks by the method described by Davey (*Ann. Trop. Med. Parasit.*, 1945, 40, in the press) but found to be inactive: 5681 and 5682 at 4 mg./50 g., and 5683 at 1 mg./50 g. In addition, 5622 was found to be inactive prophylactically at 8 mg./50 g., and 5246, which showed the highest activity against the blood forms of *P. gallinaceum* of all the 4-dialkylaminoalkylaminoquinazolines investigated, likewise showed no prophylactic activity (at 4 mg./50 g.).

Although the detailed biological results, summarised in Table I, will be published and discussed elsewhere, it may be noted that, in each of the six series of 4-dialkylaminoalkylaminoquinazolines investigated, highest activity was found in the compound containing the δ-diethylamino-α-methylbutylamino-side chain and that substitution by a chlorine atom in the 7-position led to the highest activity.

EXPERIMENTAL.

Notes on the Preparation of the Substituted Anthranilic Acids and/or their Derivatives.—Methyl 5-chloroanthranilate (as III: R' = Cl, R'' = H). Direct chlorination of methyl anthranilate (405 g.) by Freunder's method (*loc. cit.*) gave methyl 3:5-dichloroanthranilate (174 g.) and methyl 5-chloroanthranilate (200 g.). The latter had m. p. 67–69° after recrystallisation from light petroleum (b. p. 60–80°), and contained a trace of methyl anthranilate which did not interfere with the preparation of 6-chloro-4-hydroxyquinazoline.

4-Chloroanthranilic acid (III; R' = H, R'' = Cl) and 4-nitroanthranilic acid (III; R' = H, R'' = NO₂). See Curd *et al.*, forthcoming communication.

5-Methoxyanthranilic acid (III; R' = OMe, R'' = H). 2-Nitro-5-methoxybenzaldehyde (Mason, *loc. cit.*) was oxidised by alkaline permanganate at 20° to the corresponding acid in 92% yield; m. p. 132–133°. The nitro-acid was reduced to 5-methoxyanthranilic acid with hot stannous chloride and hydrochloric acid, the tin removed by addition of ammonia, a slight excess of acetic acid added to the filtrate, and the amino-acid isolated by continuous extraction with ether in a percolator; yield, 90%; m. p. 144–147° (decomp.).

2-Nitro-4-methoxybenzamide (IX) and 4-methoxyanthranilamide (X). Concentrated sulphuric acid (1 l.) and water (1 l.) were mixed and heated to boiling. 2-Nitro-4-methoxyphenyl cyanide (200 g.) (Cook *et al.*, *loc. cit.*) was then added during 2 minutes, and the mixture hand-stirred and gently boiled for 4 minutes. It was then rapidly cooled, diluted to 8 l. with ice and water, set aside for 1 hour, and the crude 2-nitro-4-methoxybenzamide (IX) collected and extracted with ammonia. The 2-nitro-4-methoxybenzoic acid (39 g.) in the extract was converted into the amide in the usual way (thionyl chloride, aqueous ammonia), and added to the main portion (m. p. 150–157°) which was then suspended in a solution of hydrated ferrous sulphate (2200 g.) in water (3 l.). The mixture was boiled and stirred, and a slight excess of ammonia gradually added. When cold, the solid was collected and extracted with boiling alcohol. The extract afforded 4-methoxyanthranilamide (X) (137 g.), m. p. 150–153°. A portion of the nitro-amide (IX) had m. p. 161–161.5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 14.6. C₉H₉O₄N₂ requires N, 14.3%). A portion of the anthranilamide (X) had m. p. 155–155.5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 17.4. C₉H₁₀O₄N₂ requires N, 16.9%).

In one reduction the amide-iron oxide mixture was dried, pulverised, and extracted with boiling acetone in an automatic apparatus. Removal of the solvent gave 2-isopropylideneamino-4-methoxybenzamide, m. p. 196–196.5° after recrystallisation from much water (charcoal) (Found: C, 63.8; H, 7.0; N, 14.0. C₁₁H₁₄O₄N₂ requires C, 64.1; H, 6.8; N, 13.6%). This anil was hydrolysed to the anthranilamide in 95% yield on boiling for 20 minutes with 25% sulphuric acid.

2-Nitro-4-methoxybenzoic acid. The cyanide (VIII) (20 g.) was refluxed for 2.5 hours with sulphuric acid (75 c.c.) and water (100 c.c.), the mixture cooled and diluted with water, and the 2-nitro-4-methoxybenzoic acid purified by dissolution in ammonia (yield, 20.4 g.); m. p. 195–197° after recrystallisation from water (charcoal).

4-Methoxyanthranilic acid (III; R' = H, R'' = OMe). This acid was prepared from 2-nitro-4-

methoxybenzoic acid in the same way as its 5-methoxy-isomer above, and was precipitated from the ammoniacal solution on addition of acetic acid. Since the amino-acid is nearly completely decarboxylated by boiling for 0.5 hour with 2*N*-hydrochloric acid, the reduction was carried out as rapidly as possible at 85–90°, and the solution then immediately cooled; yield, 85%; m. p. 166–166.5° (decomp.) after recrystallisation from water (charcoal). The methyl ester was prepared by boiling the hydrochloride of the acid with 10% methanolic hydrogen chloride for 3 hours, and purified by washing with ammonia and recrystallisation from aqueous methanol (charcoal); m. p. 75–77°.

Preparation of the 4-Hydroxyquinazolines.—4-Hydroxyquinazoline (IV; $R' = R'' = H$) was obtained in 55% yield by heating anthranilic acid (1 mol.) and formamide (2 mols.) at 135° for 3 hours and recrystallising the product from alcohol.

6-Chloro-4-hydroxyquinazoline (IV; $R' = Cl, R'' = H$) was prepared by heating methyl 5-chloroanthranilate (188 g.) and formamide (200 c.c.) at 180° for 9 hours, the methanol produced being allowed to escape. The product was extracted with cold 3% aqueous sodium hydroxide, the insoluble material (31 g.) removed, and the hydroxyquinazoline (129 g.) obtained from the extract by addition of aqueous ammonium chloride followed by recrystallisation from acetic acid. The alkali-insoluble material gave on recrystallisation from alcohol a compound, m. p. 220–221.5°, which appeared to be a 6-chloro-4-hydroxydihydroquinazoline (Found: C, 52.6; H, 3.9; N, 15.0; Cl, 19.5. $C_8H_7ON_2Cl$ requires C, 52.6; H, 3.8; N, 15.3; Cl, 19.5%).

7-Chloro-4-hydroxyquinazoline (IV; $R' = H, R'' = Cl$) was obtained in 56% yield by heating 4-chloroanthranilic acid (1 mol.) and formamide (2 mols.) at 160° for 3 hours and recrystallising the product from alcohol.

7-Nitro-4-hydroxyquinazoline (IV; $R' = H, R'' = NO_2$) was prepared by heating 4-nitroanthranilic acid (150 g.) and formamide (180 c.c.) at 160° for 6 hours, extracting the product with hot 3% aqueous sodium hydroxide, and acidifying the solution with acetic acid; yield, 152 g.

4-Hydroxy-6-methoxyquinazoline (IV; $R' = OMe, R'' = H$) was prepared by heating 5-methoxyanthranilic acid (84 g.) and formamide (100 c.c.) at 140° for 4.5 hours. The product was extracted with warm 10% aqueous sodium hydroxide, hydrochloric acid and then ammonia added, and the precipitated hydroxyquinazoline recrystallised from alcohol; yield, 75 g.

4-Hydroxy-7-methoxyquinazoline (IV; $R' = H, R'' = OMe$). (a) 4-Methoxyanthranilamide (66 g.) and formic acid (d, 1.20; 70 c.c.) were refluxed at 140° for 2.5 hours. The product was treated with 5% aqueous sodium hydroxide, and hydrochloric acid followed by ammonia added to the extract; this precipitated the hydroxyquinazoline (66 g.).

(b) Methyl 4-methoxyanthranilate (4.2 g.) and formamide (4 c.c.) were heated at 140° for 3 hours. Extraction of the product with cold, dilute sodium hydroxide gave the hydroxyquinazoline (1.3 g.) and a compound (2.2 g.), m. p. 76–78°, which was probably the unchanged ester.

(c) 4-Methoxyanthranilic acid (5 g.) and formamide (3 c.c.) were heated at 140° for 3 hours. The product, boiled with alcohol and cooled, gave the hydroxyquinazoline (1 g.). The alcoholic filtrate was evaporated, and the residue extracted with ether in the presence of aqueous sodium hydroxide. The extract gave a solid (2.4 g.), m. p. 56.5–57.5° after recrystallisation from ether–light petroleum, which appeared to be formo-*m*-anisidine (Reverdin and Luc, *Ber.*, 1914, 47, 1539, give m. p. 57°); it gave *m*-anisidine on hydrolysis with hydrochloric acid. The yield of hydroxyquinazoline was unaffected when the above reaction was carried out with a large excess of formamide. When the amino-acid (0.5 g.) and formamide (1 c.c.) were heated at 100° for 7 hours, the hydroxyquinazoline (0.03 g.) and an unidentified ammonia-soluble substance (0.15 g.), m. p. 189–190°, were obtained.

Preparation of the 4-Chloroquinazolines.—The hydroxyquinazoline (50–100 g., 1 mol.) was boiled with phosphorus pentachloride (1 mol.) and pure phosphorus oxychloride (150–300 c.c.) until the liquid was substantially clear (and no longer), the solvent removed by vacuum distillation, and the residue extracted with boiling light petroleum in a dry atmosphere. The extract deposited the 4-chloroquinazoline on cooling. This method gave products which were almost pure, and were collected as soon as the liquid was cold; otherwise, they tended to decompose. In this way, the following compounds were obtained, the reaction time, the b. p. of the light petroleum used for their isolation, and the yield being indicated in parenthesis: 4-chloroquinazoline (V; $R' = R'' = H$) (2 hours, 60–80°, 45%); 4:6-dichloroquinazoline (V; $R' = Cl, R'' = H$) (3 hours, 80–100°, 90%); 4:7-dichloroquinazoline (V; $R' = H, R'' = Cl$) (1 hour, 80–100°, 60%); 4-chloro-7-nitroquinazoline (V; $R' = H, R'' = NO_2$) (0.5 hour, 80–100°, 70%); 4-chloro-6-methoxyquinazoline (V; $R' = OMe, R'' = H$) (1.5 hours, 40–60°, 57%); 4-chloro-7-methoxyquinazoline (V; $R' = H, R'' = OMe$) (0.25 hour, 60–80°, 50%).

Preparation of the 4-Dialkylaminoalkylaminoquinazolines.—The appropriate 4-chloroquinazoline (10 g., 1 mol.) and the appropriate amine (1.1 mols.) were refluxed in alcohol (50 c.c.) for 0.5–1 hour; the required reaction had then occurred quantitatively. The material was then worked up in either of two ways: (a) the crystalline 4-dialkylaminoalkylaminoquinazoline monohydrochlorides, which were occasionally deposited during the initial refluxing, were isolated either by direct addition of ether or by concentration and dissolution of the resulting syrup in acetone followed, if necessary, by addition of ether. Reference to these salts in Table II indicates when this method of working up was used for the particular compound in question. (b) The solutions were freed from solvent, the residues were taken up in acidulated water, sodium hydroxide was added, and the liberated bases were isolated by extraction with chloroform. When the bases were so hygroscopic as to be difficult to manipulate, or when it was desired to purify them through their salts, they were converted into their disulphates by dissolution in excess of concentrated alcoholic sulphuric acid followed by addition of acetone until just turbid; the salts crystallised out on being kept at 0° for a few hours.

The essential data concerning the above quinazolines and their derivatives are collected in Table II; the following notes give additional information concerning the properties and manipulation of certain of these compounds.

Simple quinazoline series. The dimethylaminopropylamino-compound was hygroscopic. The diethylaminoethoxypropylamino-compound was distilled (b. p. 196–200°/0.03 mm.) before the

TABLE II.
4-Substituted Quinazolines.

All compounds were colourless, except those of the nitro-series which were yellow (hydroxy-compound, brown).
All compounds are new except those indicated by a reference letter in the last column.

Benz-	Substituents: 4-Position.	Salt or hydrate.	S.	M. p.	Formula.	Found, %.						Analysis.						Required, %.			Ref.	
						C.	H.	N.	Cl.	S.	C.	H.	N.	Cl.	S.	C.	H.	N.	Cl.	S.		
—	OH	—	A1	213°	C ₈ H ₈ ON ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	a
—	Cl	—	B1	98—100	C ₈ H ₇ N ₂ Cl	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	b
—	NH[CH ₂] ₂ .NEt ₂	—	C1	124—125	C ₁₂ H ₁₆ N ₄	68.7	8.5	22.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CH ₂] ₂ .NMe ₂	—	B1	64—65	C ₁₂ H ₁₆ N ₄	67.4	7.5	23.3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CH ₂] ₂ .NHBu ^a	—	—	Oil	C ₁₃ H ₁₉ N ₄	70.1	8.4	21.3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CH ₂] ₂ .NBu ^a	—	B1	70—72	C ₁₃ H ₁₉ N ₄	72.4	9.2	18.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CHMe][CH ₂] ₂ .NEt ₂	—	B1	98	C ₁₇ H ₂₃ N ₅	71.6	8.8	20.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CH ₂] ₂ .O[CH ₂] ₂ .NEt ₂	—	B2	ca. 40	C ₁₇ H ₂₃ ON ₂	67.2	8.5	18.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	NH[CH ₂] ₂ .N < [CH ₂] ₄ > CH ₃	H ₂ O	B1	106	C ₁₇ H ₂₃ N ₅ .H ₂ O	66.8	8.0	19.3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6-Cl	OH	—	D2	263—265	C ₈ H ₇ ON ₂ Cl	—	—	—	19.5	—	—	—	—	—	—	—	—	—	—	19.7	—	c
"	Cl	—	B1	155—155.5	C ₈ H ₇ N ₂ Cl	—	—	—	35.4	—	—	—	—	—	—	—	—	—	—	35.7	—	c
"	NH[CH ₂] ₂ .NEt ₂	—	B3	138—138.5	C ₁₂ H ₁₆ N ₄ Cl	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CH ₂] ₂ .NMe ₂	HCl	A3	242—243	C ₁₂ H ₁₆ N ₄ Cl.HCl	53.5	6.4	20.2	11.6	—	—	—	—	—	—	—	—	—	—	11.3	—	—
"	NH[CH ₂] ₂ .NMe ₂	—	B3	123—124	C ₁₂ H ₁₆ N ₄ Cl	51.4	5.9	20.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CH ₂] ₂ .NEt ₂	HCl	A2	203—204	C ₁₂ H ₁₆ N ₄ Cl.HCl	54.7	6.8	—	11.8	—	—	—	—	—	—	—	—	—	—	11.8	—	—
"	NH[CH ₂] ₂ .NBu ^a	HCl	A2	162.5—163	C ₁₃ H ₁₉ N ₄ Cl.HCl	59.5	7.8	16.1	10.9	—	—	—	—	—	—	—	—	—	—	10.8	—	—
"	NH[CH ₂] ₂ .NBu ^a	—	B1	79—80	C ₁₃ H ₁₉ N ₄ Cl	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CHMe][CH ₂] ₂ .NEt ₂	HCl	A1	168.5—169.5	C ₁₃ H ₁₉ N ₄ Cl.HCl	59.5	7.8	16.1	—	—	—	—	—	—	—	—	—	—	—	16.1	—	—
"	NH[CH ₂] ₂ .N < [CH ₂] ₄ > CH ₃	—	B1	112—113	C ₁₇ H ₂₃ N ₅ Cl	63.7	8.0	17.3	9.1	—	—	—	—	—	—	—	—	—	—	9.2	—	—
"	NH[CH ₂] ₂ .N < [CH ₂] ₄ > CH ₃	—	B1	117—118	C ₁₇ H ₂₃ N ₅ Cl	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	c
"	"	HCl	A1	209—209.5	C ₁₃ H ₁₉ N ₄ Cl.HCl	56.7	6.5	—	10.8	—	—	—	—	—	—	—	—	—	—	10.4	—	—
7-Cl	OH	—	A1	245	C ₈ H ₇ ON ₂ Cl	53.1	3.1	15.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	Cl	—	B4	132	C ₈ H ₇ N ₂ Cl	48.5	2.4	14.4	35.5	—	—	—	—	—	—	—	—	—	—	35.7	—	—
"	NH[CH ₂] ₂ .NEt ₂	—	B1	125	C ₁₂ H ₁₆ N ₄ Cl	60.3	6.9	20.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CH ₂] ₂ .NMe ₂	—	B1	102	C ₁₂ H ₁₆ N ₄ Cl	59.4	6.2	21.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CH ₂] ₂ .NEt ₂	—	B1	105	C ₁₂ H ₁₆ N ₄ Cl	61.6	7.2	19.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CH ₂] ₂ .NBu ^a	—	B1	81—82	C ₁₃ H ₁₉ N ₄ Cl	65.1	8.4	16.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	NH[CHMe][CH ₂] ₂ .NEt ₂	—	B1	104—105	C ₁₃ H ₁₉ N ₄ Cl	63.8	7.7	17.8	—	—	—	—	—	—	—	—	—	—	—	17.5	—	—
"	NH[CH ₂] ₂ .O[CH ₂] ₂ .NEt ₂	—	B1	69—70	C ₁₇ H ₂₃ ON ₂ Cl	60.9	7.7	16.9	—	—	—	—	—	—	—	—	—	—	—	16.6	—	—
"	NH[CH ₂] ₂ .N < [CH ₂] ₄ > CH ₃	0.5H ₂ O	B1	130—131	C ₁₇ H ₂₃ ON ₂ Cl.0.5H ₂ O	61.3	7.3	18.1	—	—	—	—	—	—	—	—	—	—	—	17.9	—	—
7-NO ₂	OH	—	D1	269—270	C ₈ H ₇ ON ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	Cl	—	B4	146—147	C ₈ H ₇ ON ₂ Cl	—	—	—	16.6	—	—	—	—	—	—	—	—	—	—	16.9	—	—
"	NH[CH ₂] ₂ .NEt ₂	—	E1	151—151.5	C ₁₂ H ₁₆ ON ₂ N ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	"	HCl	A3	213—214	C ₁₂ H ₁₆ ON ₂ N ₂ .HCl	51.7	6.4	21.4	10.7	—	—	—	—	—	—	—	—	—	—	24.2	—	—
"	"	—	E1	132—132.5	C ₁₂ H ₁₆ ON ₂ N ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21.5	—	—
"	"	HCl	A3	238—239	C ₁₂ H ₁₆ ON ₂ N ₂ .HCl	—	—	—	—	—	—	—	—	—	—	—	—	—	—	25.5	—	—
"	NH[CH ₂] ₂ .NMe ₂	—	E1	132—132.5	C ₁₂ H ₁₆ ON ₂ N ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	"	HCl	A3	238—239	C ₁₂ H ₁₆ ON ₂ N ₂ .HCl	50.3	5.7	25.5	11.6	—	—	—	—	—	—	—	—	—	—	—	11.4	—
"	"	—	E1	132—132.5	C ₁₂ H ₁₆ ON ₂ N ₂	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
"	"	HCl	A3	238—239	C ₁₂ H ₁₆ ON ₂ N ₂ .HCl	50.3	5.7	25.5	11.6	—	—	—	—	—	—	—	—	—	—	—	11.4	—

recrystallisation indicated in Table II. The monobutylaminopropylamino-compound had b. p. 150—170°/0.0001 mm.

6-Chloroquinazoline series. During m. p. determinations on the diethylaminopropylamino-hydrochloride the melt occasionally solidified and then remelted at 186—187°. In the preparation of the dibutylaminopropylamino-hydrochloride, the cooled reaction mixture deposited waxy plates of a compound which had the same composition as γ -dibutylaminopropylamine dihydrochloride; m. p. 326—327° (decomp.) after recrystallisation from alcohol containing a trace of water (Found: C, 50.8; H, 11.1; N, 10.4; ionic Cl, 27.9. $C_{11}H_{20}N_2 \cdot 2HCl$ requires C, 51.0; H, 10.8; N, 10.8; ionic Cl, 27.4%). Evidence that it was not identical with this diamine salt is: (a) a high m. p. and sparing solubility in pure alcohol would not be expected for such a salt; (b) addition of sodium hydroxide to its aqueous solution precipitated an almost odourless oil; (c) γ -dibutylaminopropylamine dihydrochloride was obtained, either by confinement over solid sodium hydroxide of a solution of the base in a slight excess of concentrated hydrochloric acid or by passing dry hydrogen chloride into a solution of the base in absolute ether, as an uncrystallisable syrup, an alcoholic solution of which failed to crystallise after being kept for several weeks, either alone or after being seeded with the unidentified compound. The latter was encountered during the preparation of all the dibutylaminopropylaminoquinazolines reported in this paper, and evidently arose from an impurity in the γ -dibutylaminopropylamine used.

7-Nitroquinazoline series. The diethylaminopropylamino-, diethylaminomethylbutylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases became dark brown on exposure to light. The last compound was hygroscopic, and formed a syrup on exposure to air. The syrup, which was a monohydrate, ultimately crystallised, and the pure anhydrous base was prepared from the purified hydrate by desiccation over sulphuric acid.

6-Methoxyquinazoline series. On very humid days the diethylaminopropylamino- and dibutylaminopropylamino-bases were hygroscopic, rapidly forming syrups on exposure to air. The piperidinopropylamino-disulphate underwent marked dissociation to the monosulphate on recrystallisation from slightly aqueous alcohol; the dibutylaminopropylamino-disulphate also dissociated when recrystallised in the absence of free sulphuric acid, although much less readily than the previous salt. The diethylaminomethylbutylamino-base monohydrate withstood the drying action of sulphuric acid, and hence must have considerable stability.

7-Methoxyquinazoline series. The diethylaminopropylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases were hygroscopic, and formed syrups on exposure to air. The syrup from the last compound crystallised as the monohydrate on standing, and the pure anhydrous base was obtained from the purified monohydrate by confinement in a vacuum over sulphuric acid. The dibutylaminopropylamino-base could not be satisfactorily recrystallised, and was therefore prepared from its purified disulphate by basification, extraction with pure ether, and removal of solvent, finally in a desiccator over sulphuric acid. The diethylaminomethylbutylamino-base was hygroscopic to an extent depending on the climatic conditions, and was purified through its oxalate as follows: the crude base, dissolved in acetone, was added to excess of a dilute solution of hydrated oxalic acid in acetone. Next day, the acetone was decanted, and the hard residue boiled with alcohol to give a crystalline solid, m. p. 166—167° (decomp.) unchanged after recrystallisation from alcohol containing a trace of water. The constitution of this compound was uncertain, but it appeared to be either the base mono-oxalate monoalcoholate monohydrate or the dihydrated monoethyl oxalate salt of the base (Found for material dried in a vacuum over sulphuric acid: C, 55.9; H, 7.9; N, 12.0. $C_{11}H_{18}ON_2 \cdot C_2H_2O_4 \cdot C_2H_5O \cdot H_2O$ or $C_{11}H_{18}ON_2 \cdot C_2H_5O \cdot 2H_2O$ requires C, 56.2; H, 8.1; N, 11.9%). The base was recovered from this salt by dissolution in water, addition of sodium hydroxide, and extraction with pure ether.

2-Chloro-4- β -diethylaminoethylaminoquinazoline (XI; R = NH \cdot [CH $_2$] $_2$ ·NEt $_2$).—A mixture of 2:4-dichloroquinazoline (6 g.), β -diethylaminoethylamine (4 g., 1.1 mols.), and alcohol (25 c.c.) was refluxed for 30 minutes. After cooling, the hydrochloride of the quinazoline (XI; R = NH \cdot [CH $_2$] $_2$ ·NEt $_2$) which had separated was collected and crystallised from alcohol (yield, 90%), m. p. 202° in agreement with Curd, Landquist, and Rose (Part XIV, *loc. cit.*) (Found: N, 17.5. Calc. for $C_{14}H_{19}N_4Cl \cdot HCl$: N, 17.8%).

2-Amino-4- β -diethylaminoethylaminoquinazoline (XII; R = NH \cdot [CH $_2$] $_2$ ·NEt $_2$).—Several experiments in which the degree and period of heating were varied showed the following conditions to be the most satisfactory. The above hydrochloride (10 g.) was dissolved in a minimum amount of warm alcohol and then treated with cold alcohol previously saturated with ammonia (50 c.c.). The solution was filtered to remove precipitated ammonium chloride and then heated at 120° for 2 hours. Alcohol and ammonia were then removed from the product by evaporation at 20 mm. pressure, the residue was treated with 30% aqueous sodium hydroxide, and the base extracted with ether and dried (K $_2$ CO $_3$). After removal of the ether, the residual solid was first extracted with hot light petroleum (b. p. 60—80°) to remove unchanged chloro-compound, and then recrystallised from acetone. The 2-aminoquinazoline was obtained as colourless crystals, m. p. 144° (Found: C, 65.3; H, 8.2; N, 26.8. $C_{14}H_{19}N_5$ requires C, 64.9; H, 8.1; N, 27.0%).

When this reaction was carried out at higher temperatures, e.g., 170°, intractable gummy mixtures were produced, from which the only pure constituent isolated was 2:4-dihydroxyquinazoline.

2-Chloro-4- δ -diethylamino- α -methylbutylaminoquinazoline (XI; R = NH·CHMe·[CH $_2$] $_3$ ·NEt $_2$).—A mixture of 2:4-dichloroquinazoline (10 g.), δ -diethylamino- α -methylbutylamine (8 g., 1.1 mols.), and alcohol (50 c.c.) was refluxed for 1 hour, and the alcohol then evaporated. The residual syrup was treated with 30% aqueous sodium hydroxide, and the liberated base extracted with ether and dried. Evaporation of the ether gave an oily residue which solidified when vigorously stirred with chilled light petroleum (b. p. 40—60°); recrystallisation from light petroleum then furnished the 2-chloro-compound as colourless crystals, m. p. 98° (Found: C, 63.7; H, 8.0; N, 17.8. Calc. for $C_{17}H_{25}N_4Cl$: C, 63.7; H, 7.8; N, 17.5%) (yield, 37%).

2:4-Dihydroxy-7-methoxyquinazoline and its Derivatives.—Sodium cyanate (2.5 g.) was added rapidly to a suspension of pure 4-methoxyanthranilic acid (5 g.) in acetic acid (15 c.c.) at 60°. The mixture was heated on the steam-bath until effervescence ceased, diluted with water, and the 2-carbamido-4-methoxy-

benzoic acid collected, washed with boiling alcohol to remove any traces of unchanged amino-acid, and further purified by dissolution in ammonia and reprecipitation with acetic acid; m. p. 185–186° (decomp.) (Found: N, 13.1. $C_9H_{10}O_4N_2$ requires N, 13.3%). The carbamido-acid was then boiled for 1 minute with 20% sodium hydroxide (30 c.c.), cooled, and the sodium salt of the dihydroxyquinazoline collected. The salt was dissolved in boiling water, dilute sulphuric acid followed by ammonia added, and the precipitated 2:4-dihydroxy-7-methoxyquinazoline collected and washed with alcohol (yield, 4.3 g.); m. p. 299–301° (Found: N, 14.4. $C_9H_8O_3N_2$ requires N, 14.6%).

The dihydroxyquinazoline (10 g.), phosphorus pentachloride (22 g.), and pure phosphorus oxychloride (32 c.c.) were boiled until the liquid was clear (10 minutes), the solvent distilled off under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60–80°) in a dry atmosphere. 2:4-Dichloro-7-methoxyquinazoline (7 g.) crystallised from the extract on cooling; m. p. 121–121.5° after recrystallisation from light petroleum (b. p. 60–80°) (Found: N, 12.2; Cl, 30.9. $C_9H_6ON_2Cl_2$ requires N, 12.2; Cl, 31.0%).

The dichloroquinazoline (5 g.) and β -diethylaminoethylamine (3.1 g., 1.2 mols.) were refluxed in alcohol (25 c.c.) for 10 minutes, the solvent was removed, the crystalline residue dissolved in water, aqueous sodium hydroxide added, and the liberated 2-chloro-4- β -diethylaminoethylamino-7-methoxyquinazoline isolated by extraction with chloroform and recrystallised from light petroleum (b. p. 60–80°) (yield, 5.8 g.); m. p. 108–109° (Found: N, 17.9; Cl, 11.4. $C_{16}H_{21}ON_4Cl$ requires N, 18.2; Cl, 11.5%).

The above chloroalkylamino-compound (1 g.) and alcohol saturated with ammonia at 0° (9 c.c.) were heated in a sealed tube at 160° for 3 hours. The solution was then distilled to remove solvent and ammonia, and the resulting syrup dissolved in dilute hydrochloric acid, basified with sodium hydroxide, and extracted with ether. Removal of the solvent left a small amount of resinous material which could not be crystallised, and from which crystalline salts could not be obtained.

This investigation was carried out as part of a wartime programme of antimalarial research sponsored by the Medical Research Council in collaboration with Imperial Chemical Industries Ltd. We are indebted to the former for grants (N. B. C. and G. M. G.) and to the latter for materials and for carrying out the biological tests. We are also greatly indebted to the workers of Imperial Chemical Industries for many discussions on the above work.

After this paper had been prepared for publication the following papers on quinazoline derivatives of related types appeared: Endicott, Wick, Mercury, and Sherrill (*J. Amer. Chem. Soc.*, 1946, **68**, 1299); Smith, Elisberg, and Sherrill (*ibid.*, p. 1301); Endicott, Alden, and Sherrill (*ibid.*, p. 1303); Price, Leonard, and Curtin (*ibid.*, p. 1305); Christensen, Graham, and Tomisek (*ibid.*, p. 1306), and Bunnett (*ibid.*, p. 1327).

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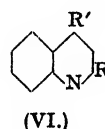
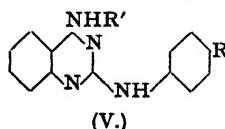
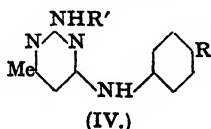
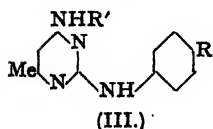
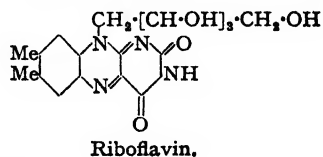
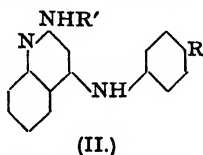
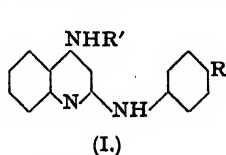
[Received, September 10th, 1946.]

167. Synthetic Antimalarials. Part XVII. Some Arylamino-aminoalkylaminoquinoline Derivatives.

By F. H. S. CURD, C. G. RAISON, and F. L. ROSE.

The differential reactivities of the substituent groups in 2:4-dihydroxy- and 2:4-dichloroquinoline have been investigated and have been utilised for the preparation of a series of 2-arylamino-4-aminoalkylaminoquinolines (I) and their isomers (II). The former show the higher degree of antimalarial activity against *P. gallinaceum* in chicks, and this is discussed in the light of recent hypotheses.

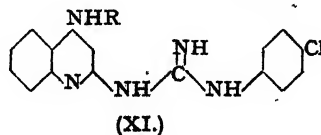
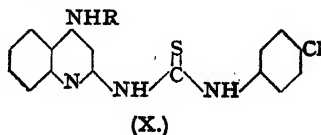
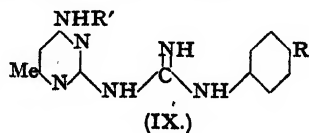
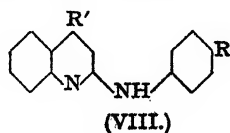
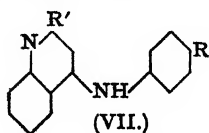
THE purpose of this communication is to report work leading to the synthesis of quinoline derivatives of types (I and II; $R' = \text{aminoalkyl}$) that have not hitherto been investigated in the search for antimalarials based on the quinoline nucleus. The new compounds have an



arylamino- and an aminoalkylamino-group attached to a heterocyclic ring system and in this respect are related to the pyrimidines of types (III) and (IV) described in Parts I, II, VI, and IX (*J.*, 1946, 343, 351, 370, 720) and the 2-arylamino-4-aminoalkylaminoquinazolines (V) (Part XIV, this vol., p. 775), all of which are actively plasmodicidal.

To achieve the synthesis of compounds of types (I) and (II) the possibility of a stepwise replacement of the groups R and R' in a quinoline derivative of type (VI; R = R' = OH or halogen) was first considered because the simplest of such compounds, namely 2:4-dihydroxyquinoline, was available as a dye intermediate. Further, literature methods were available for the preparation of a considerable number of nuclear substituted derivatives. Very little information was available, however, on the feasibility of carrying out the desired stepwise replacements. The reaction of 2:4-dihydroxyquinoline with a number of primary and secondary aliphatic amines at temperatures of 150—250° to give exclusively 4-amino- or 4-alkylamino-quinolines in high yields has been described (G.P. 681980). A similar reaction has now been found to occur with dialkylaminoalkylamines such as γ -diethylaminopropylamine giving 4- γ -diethylaminopropylamino-2-hydroxyquinoline (VI; R = OH, R' = NH·[CH₂]₃·NEt₂). This compound reacted slowly with boiling phosphoryl chloride to give 2-chloro-4- γ -diethylaminopropylaminoquinoline (VI; R = Cl, R' = NH·[CH₂]₃·NEt₂) which was then condensed with *p*-chloroaniline by heating the reactants at ca. 200° for several hours, the product being 2-*p*-chloroanilino-4- γ -diethylaminopropylaminoquinoline (I; R = Cl, R' = [CH₂]₃·NEt₂). The condensation was also possible using an equimolecular proportion of *p*-chloroaniline in aqueous suspension in presence of hydrochloric acid (1·1 mols.), but a reaction time of 48 hours was needed to achieve a good yield. The orientation of these derivatives was demonstrated by the smooth reduction of the intermediate 2-chloro-4- γ -diethylaminopropylaminoquinoline with hydrogen and Raney nickel (cf. Whitmore and Revukas, *J. Amer. Chem. Soc.*, 1940, 62, 1691; Krahler and Burger, *ibid.*, 1941, 63, 2367) to give 4- γ -diethylaminopropylaminoquinoline, identical with a specimen prepared by the condensation of γ -diethylaminopropylamine with 4-chloroquinoline.

G.P. 681980 makes no mention of the condensation of 2:4-dihydroxyquinoline with arylamines, and we have found that the former is recovered completely unchanged after being heated with excess of aniline at 180—200° for 48 hours. In the presence of aniline hydrochloride, however, a smooth reaction occurred with the elimination of water and the formation (in 90% yield) of 4-anilino-2-hydroxyquinoline (VII; R = H, R' = OH). Even so weak an acid as boric acid catalysed the condensation but less efficiently than hydrochloric acid. This compound has been described previously by v. Niementowski (*Ber.*, 1907, 40, 4285) and by Dziewonski and Dymek (*Chem. Zentr.*, 1937, I, 1153). The former obtained it as one product of the reaction of benzoylacetic ester with anthranilic acid, noted its insolubility in alkali, and obtained 4-anilinoquinoline in poor yield from it on distillation with zinc dust. The latter authors heated 2:4-dianilinoquinoline with potassium hydroxide, obtained 4-anilino-2-hydroxyquinoline, and in addition the isomeric 2-anilino-4-hydroxyquinoline which is alkali soluble. They apparently used v. Niementowski's work as a basis for the orientation of the two isomers. We have found that 4-anilino-2-hydroxyquinoline reacts readily with phosphoryl chloride to yield 2-chloro-4-anilinoquinoline, and this compound, on reduction with hydrogen and Raney nickel, gave 4-anilinoquinoline, m. p. 196—198°, identical with an authentic specimen prepared from 4-chloroquinoline (cf. Ephraim, *Ber.*, 1893, 26, 2229; Backeberg, *J.*, 1933, 618). The corresponding *p*-chloroanilino-compound (VII; R = R' = Cl) was similarly obtained by first bringing 2:4-dihydroxyquinoline into reaction with *p*-chloroaniline in presence of its



hydrochloride to give 4-*p*-chloroanilino-2-hydroxyquinoline (VII; R = Cl, R' = OH) and then treating this with phosphoryl chloride. The 2-chloro-4-*p*-chloroanilinoquinoline thus obtained reacted readily with β -diethylaminoethylamine at 130—140° to give 4-*p*-chloroanilino-2- β -diethylaminoethylaminoquinoline and with γ -di-*n*-butylaminopropylamine to give 4-*p*-chloroanilino-2- γ -di-*n*-butylaminopropylaminoquinoline which were most readily isolated as their dihydriodides.

The reactions described above sufficed for the preparation of the two isomeric types of quinoline derivatives (I) and (II) of undoubted orientation, but before they were fully worked out a number of compounds of type (I) had been prepared starting from 2 : 4-dichloroquinoline. As far as we are aware the relative reactivities of the halogen atoms in this compound have been investigated previously only by Buchmann and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1357) who heated it with potassium hydroxide in alcohol. Besides a small amount of 4-chlorocarbostyryl they obtained approximately equal amounts of 4-chloro-2-ethoxy- and 2-chloro-4-ethoxy-quinoline. The reaction of (VI; $R = R' = Cl$) with arylamines has now been investigated. When heated with an equimolecular amount of aniline, in alcohol or benzene in presence of anhydrous potassium carbonate, no reaction took place. This failure was understandable when it was found that the reaction of 2 : 4-dichloroquinoline and arylamines was catalysed by acid, so that in view of the formation of hydrochloric acid by the reaction the process was normally autocatalytic and indeed, in the absence of solvent, often violently exothermic. These general observations were later given confirmation by the work of Banks (*ibid.*, 1944, **66**, 1127). When equimolecular amounts of 2 : 4-dichloroquinoline and aniline, in acetic acid solution, were warmed together on the steam-bath, only a mildly exothermic reaction took place. The product was a mixture, but the only pure compound that could be isolated (in 53% yield) was 4-chloro-2-anilinoquinoline. This gave a considerable depression in melting point with 2-chloro-4-anilinoquinoline, whilst on reduction with hydrogen and Raney nickel it gave a substance, m. p. 102—103°, conforming to the description of 2-anilinoquinoline recorded in the literature (Friedländer and Weinberg, *Ber.*, 1885, **18**, 1532; Goldschmidt and Meissler, *ibid.*, 1890, **23**, 277). A number of other arylamines were then condensed with 2 : 4-dichloroquinoline to give products of type (VIII; $R' = Cl$) which on heating with aminoalkylamines afforded compounds of type (I). Thus (VI; $R = R' = Cl$) and *p*-chloroaniline led to 4-chloro-2-*p*-chloroanilinoquinoline which when condensed with γ -diethylaminopropylamine gave (I; $R = Cl$, $R' = [CH_2]_3 \cdot NEt_3$) identical with that made from 2-chloro-4- γ -diethylaminopropylaminoquinoline and *p*-chloroaniline.

When tested against *P. gallinaceum* in chicks, 2-*p*-chloroanilino-4- β -diethylaminoethylamino- and 4- γ -diethylaminopropylamino-quinoline showed activity comparable with that of the analogous pyrimidines of type (III) but a certain lack of parallelism between the two series was observed when further variations in the arylamino- and aminoalkylamino-groups were investigated. An even greater divergence was noticeable between the quinoline derivatives of type (II) and the pyrimidine derivatives of type (IV), for the high activity of (IV; $R = Cl$, $R' = [CH_2]_3 \cdot NBu_3^a$) (Part VI, *loc. cit.*) contrasted most markedly with the very low order of activity shown by (II; $R = Cl$, $R' = [CH_2]_3 \cdot NBu_3^a$). This led us to examine the possibility that the activity of compounds of type (I) might be unconnected with their relationship to type (III), and this appeared to be a likely possibility since quinolines of types (I) and (II) do not allow conjugation between the pendant aryl and aminoalkyl groups *via* alternate carbon and nitrogen atoms as a result of either prototropy or resonance which, from our earlier work, we had come to believe might be a significant factor in the activity of our pyrimidine and diguanide types (Part XII, this vol., p. 154).

Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has reported that 4- δ -diethylamino- α -methylbutylamino-6-methoxyquinoline possesses antimalarial properties, and other work carried out in these laboratories (to be published) had shown that 4-dialkylaminoalkylaminoquinolines in general possessed such properties. It therefore seemed conceivable that the activity of quinolines of type (I) might be due to their being 4-dialkylaminoalkylaminoquinolines carrying a grouping in the 2-position which made no direct contribution to the antimalarial activity and at the same time was not markedly deactivating. This possibility was further illustrated by the antimalarial results obtained with some of the intermediates, containing a dialkylaminoalkylamino-group in the 4-position, used in the synthetic work described in this paper. Thus whereas 4- γ -diethylaminopropylamino-2-hydroxy- and 2-chloro-4- γ -diethylaminopropylamino-quinoline were without activity at high doses, 2-amino-4- β -diethylaminoethylaminoquinoline and the corresponding γ -diethylaminopropylamino-derivative (VI; $R = NH_2$, $R' = NH \cdot [CH_2]_3 \cdot NEt_3$) (see later) showed considerable antimalarial activity. In this connection the work of Gilman and Spatz (*Iowa State College J. Sci.*, 1942, **17**, 129; *J. Amer. Chem. Soc.*, 1944, **66**, 621), knowledge of which only reached us when our own work was largely completed, is perhaps relevant. They have reported activity in certain 4-dialkylaminoalkylamino-2-arylquinolines prepared as "open chain models" of mepacrine, but do not provide any substantial proof that the activity of the compounds is in fact due to their relationship to mepacrine. They can equally well be regarded simply as modified 4-dialkylaminoalkylaminoquinolines.

This point was examined further in respect of our own compounds by observing the effect on antimalarial activity of introducing substituents into type (I) with and without the presence of the 2-arylamino-group. Compounds of the latter type are described in G.P. 683692 and E.P. 481874, and we were ourselves at the time collecting information on such compounds. For this purpose we prepared 2-*p*-chloroanilino-4- γ -diethylaminopropylamino-7:8-benzo-, 7-chloro-2-*p*-chloroanilino-4- γ -diethylaminopropylamino-, and 2-*p*-chloroanilino-4- γ -diethylaminopropylamino-3-methyl-quinoline. 2:4-Dichloro-7:8-benzoquinoline did not react with *p*-chloroaniline in acetic acid solution on the steam-bath, but from the product obtained by heating the two reactants together in 2-ethoxyethanol at 160°, 4-chloro-2-*p*-chloroanilino-7:8-benzoquinoline, was obtained, in rather poor yield, and condensed with γ -diethylaminopropylamine. Methyl 4-chloroanthranilate was condensed with ethyl malonate in the presence of sodium methoxide and the product hydrolysed and decarboxylated to give 7-chloro-2:4-dihydroxyquinoline which was successively condensed with γ -diethylaminopropylamine and treated with phosphoryl chloride to yield 2:7-dichloro-4- γ -diethylaminopropylaminoquinoline; this reacted with *p*-chloroaniline to give 7-chloro-2-*p*-chloroanilino-4- γ -diethylaminopropylaminoquinoline. In attempting to prepare compounds of type (I) containing an additional 3-methyl or 3-ethyl substituent, difficulties were encountered which were probably due to steric hindrance. Both 2:4-dihydroxy-3-methyl- and -3-ethyl-quinoline condensed with γ -diethylaminopropylamine to give the expected 4- γ -diethylaminopropylamino-2-hydroxy-derivatives which when treated with phosphoryl chloride gave respectively 2-chloro-4- γ -diethylaminopropylamino-3-methyl- and -3-ethyl-quinoline; but whereas the former on heating with *p*-chloroaniline gave a product from which the desired 2-*p*-chloroanilino-4- γ -diethylaminopropylamino-3-methylquinoline could be isolated, the latter gave an intractable mixture. Further, both 2:4-dichloro-3-methyl- and -3-ethyl-quinoline condensed with *p*-chloroaniline in acetic acid solution at 100° to give respectively 4-chloro-2-*p*-chloroanilino-3-methyl- and -3-ethyl-quinoline, but, although the former condensed slowly with γ -diethylaminopropylamine at 190–200°, the latter hardly reacted with this amine or with β -diethylaminoethylamine at this temperature and at higher temperatures (up to 250° in sealed tubes) gave intractable products.

The antimalarial activities obtained with these compounds (see Table I) did not support the view that they functioned simply as modified 4-dialkylaminoalkylaminoquinolines, and the possibility, mentioned earlier, that they might then be related biologically to the pyrimidines of type (III) was re-examined.

In a previous paper in this series (Curd and Rose, *J.*, 1946, 362) it was shown that the antimalarial activity of compounds of type (III) was retained and in certain instances enhanced if the arylamino- was replaced by an arylguanidino-group to give type (IX). A similar modification was accordingly made in the quinolines of type (I) utilising a synthetic method originally worked out as an alternative procedure for the synthesis of compounds of type (IX) and related compounds, which we shall report in detail later. A 2-chloro-4-dialkylaminoalkylaminoquinoline was treated with ammonia in hot phenol to give the corresponding 2-amino-4-dialkylaminoalkylaminoquinoline (VI; R = NH₂, R' = dialkylaminoalkylamino) which was then condensed with *p*-chlorophenyl isothiocyanate. The 2-*p*-chlorophenylthioureido-compound (X) thus obtained was desulphurised in the presence of alcoholic ammonia by means of mercuric oxide to give the 2-*p*-chlorophenylguanidino-derivative (XI). 2-*p*-Chlorophenylguanidino-4- β -diethylaminoethylamino- and -4- γ -diethylaminopropylamino-quinoline were prepared in this way, but both failed to show antimalarial activity at tolerated doses. The corresponding thioureido-compounds of type (X) were likewise without demonstrable activity.

Attempts to prepare compounds of type (XI) by condensation of the appropriate 2-chloro-4-dialkylaminoalkylaminoquinoline with *p*-chlorophenylguanidine were unsuccessful. The chloroquinoline was recovered unchanged from trial condensations at temperatures at which ammonia was copiously evolved by breakdown of the guanidine.

Reviewing the results obtained with these compounds it is not possible to draw any very definite conclusion concerning the chemotherapeutic relationship of the quinolines of types (I) and (II) with the pyrimidines of types (III) and (IV) respectively. So far, we have considered this relationship only from the point of view of the chemical hypotheses followed in developing the discovery of antimalarial activity in the pyrimidine of types (III) and (IV). In earlier papers, however, we have discussed the possibility that antiplasmodial activity of these latter types may be associated with a growth antagonism arising from their formal structural similarity to the riboflavin molecule. Examination of the formulæ of (I) and (II) on this basis shows the former to bear the closer structural resemblance to the growth factor. This holds whether the pyrimidine ring of (I) is considered to correspond to the pyrimidine ring or to the benzene ring of

TABLE I.

Antimalarial activities.

The activities are the results of tests against *P. gallinaceum* in chicks and are expressed in the same way as in Part I (*J.*, 1946, 343). The full biological results will be published elsewhere.

Ref. No.	Substance.	Dose (mg./kg.).	Activity.
3627	4- <i>p</i> -Chloroanilino-2- β -diethylaminoethylaminoquinoline dihydriodide	400	+
3628	2- <i>p</i> -Chloroanilino-4- β -diethylaminoethylaminoquinoline dihydriodide	120	++
		80	+ to ++
		40	+
4006	2- <i>p</i> -Chloroanilino-4- β -diethylaminoethylaminoquinoline dihydrochloride	60	+
		40	\pm
		20	—
4011	2- <i>p</i> -Chloroanilino-4- γ -diethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4321	2- <i>p</i> -Anisidino-4- β -diethylaminoethylaminoquinoline dihydriodide	120	+
		80	+
4322	2- <i>p</i> -Toluidino-4- β -diethylaminoethylaminoquinoline	100	++
		50	+
4323	2- β -Naphthylamino-4- β -diethylaminoethylaminoquinoline dihydriodide	160	+
		80	+
4324	2- <i>p</i> -Chloroanilino-4- γ -diethylaminopropylamino-7 : 8-benzoquinoline dihydrochloride	400	—
4342	2- <i>p</i> -Chloroanilino-4- γ -dimethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4385	2- <i>p</i> -Chloroanilino-4- γ -piperidinopropylaminoquinoline dihydrochloride	60	+ to ++
		40	—
4612	2- <i>p</i> -Nitroanilino-4- γ -diethylaminopropylaminoquinoline dihydrochloride	80	+ to ++
		40	—
4623	7-Chloro-2- <i>p</i> -chloroanilino-4- γ -diethylaminopropylaminoquinoline	160	+
		80	+
		40	+
4627	4- <i>p</i> -Chloroanilino-2- γ -di- <i>n</i> -butylaminopropylaminoquinoline dihydriodide	400	+
		200	\pm
4665	2- <i>p</i> -Chloroanilino-4- δ -diethylaminobutylaminoquinoline dihydrochloride	80	+ to ++
		60	+
		40	+
4921	2-(6'-Bromo- β -naphthylamino)-2- γ -diethylaminopropylaminoquinoline	120	+
5092	2- <i>p</i> -Chloroanilino-4- γ -diethylaminopropylamino-3-methylquinoline	160	+
		80	—
5129	2- <i>p</i> -Chloroanilino-4- δ -diethylamino- α -methylbutylaminoquinoline	80	+
		40	+
5226	2- <i>p</i> -Chlorophenylthioureido-4- γ -diethylaminopropylaminoquinoline	160	—
		80	—
5276	2- <i>p</i> -Chlorophenylguanidino-4- γ -diethylaminopropylaminoquinoline	80	—
		40	—
5463	2- <i>p</i> -Chlorophenylthioureido-4- β -diethylaminoethylaminoquinoline	160	—
		80	—
5477	2- <i>p</i> -Chlorophenylguanidino-4- β -diethylaminoethylaminoquinoline	160	—
		80	—
3738	4- γ -Diethylaminopropylamino-2-hydroxyquinoline	600	—
5099	2-Chloro-4- γ -diethylaminopropylaminoquinoline	160	—
5123	2-Amino-4- γ -diethylaminopropylaminoquinoline	80	++
		40	+
		20	—
5534	2-Amino-4- β -diethylaminoethylaminoquinoline	80	++
		40	++

riboflavin (in the latter case the fused benzene ring of the quinoline nucleus will correspond to the 6 : 7-dimethyl grouping in riboflavin, and examples of such a biological equivalence are provided among the polycyclic carcinogenic substances). This view affords some explanation of the variations in biological activity which occur on further substitution or modification of type (I). For instance, while type (IX) retains the property of being able to function as a riboflavin antagonist, the conversion of type (I) into type (XI) probably increases the total dimensions of the molecule to such an extent that a relationship with riboflavin is no longer discernible.

EXPERIMENTAL.

4- γ -Diethylaminopropylamino-2-hydroxyquinoline (VI; R = OH, R' = NH·[CH₂]₂·NEt₃).—2 : 4-Dihydroxyquinoline (32.2 g., 1 mol.) and γ -diethylaminopropylamine (52 g., 2 mols.) were heated under reflux by means of an oil-bath at 170–180° for 18 hours. The cooled mixture was lixiviated

with water, and the product collected and washed with water. It was then extracted with dilute acetic acid and the filtered extract made alkaline with ammonia to reprecipitate the compound as an oil which rapidly solidified (yield, 68%). It formed colourless needles from aqueous alcohol, m. p. 174—175° (Found: C, 70.9; H, 8.6; N, 15.3. $C_{18}H_{22}ON_2$ requires C, 70.3; H, 8.4; N, 15.4%). It is insoluble in alkalis.

4- β -Diethylaminoethylamino-2-hydroxyquinoline (VI; R = OH, R' = NH \cdot [CH $_2$] $_2$ ·NEt $_2$).—2:4-Dihydroxyquinoline (80 g.) and β -diethylaminoethylamine (84 g., 1.45 mols.) were heated under reflux with stirring at 170—180° for 27 hours. After cooling, the mixture was extracted with dilute acetic acid and filtered from insoluble material (unchanged 2:4-dihydroxyquinoline, 32.6 g.). The acetic acid extract was made alkaline with ammonia which precipitated the product as an oil. This gradually solidified (yield, 56.8 g.), and subsequent purification by crystallisation from aqueous acetone gave 4- β -diethylaminoethylamino-2-hydroxyquinoline, m. p. 61—63° (Found: C, 61.1; H, 8.4; N, 13.8. $C_{18}H_{22}ON_2 \cdot 2H_2O$ requires C, 61.0; H, 8.5; N, 14.2%).

2-Chloro-4- γ -diethylaminopropylaminoquinoline (VI; R = Cl, R' = NH \cdot [CH $_2$] $_3$ ·NEt $_2$).—4- γ -Diethylaminopropylamino-2-hydroxyquinoline (134 g.) and phosphoryl chloride (268 c.c.) were boiled under reflux for 20 hours and the solution cooled and poured on ice. The oil liberated on basification with 40% potassium hydroxide solution was extracted with ether and the ethereal extract filtered, dried (Na $_2$ SO $_4$), and evaporated. The residual chloro-compound, purified by vacuum distillation, had b. p. 193—194°/0.2 mm., 180—182°/0.08 mm., and crystallised on standing (yield, 68%). It then separated from light petroleum (b. p. 40—80°) as colourless prisms, m. p. 51—52° (Found: C, 66.0; H, 7.4; N, 14.4; Cl, 12.1. $C_{18}H_{22}N_2Cl$ requires C, 65.9; H, 7.55; N, 14.4; Cl, 12.2%). The dipicrate crystallised from 2-ethoxyethanol in fine yellow needles, m. p. 193—194° (Found: N, 16.5; Cl, 4.8. $C_{18}H_{22}N_2Cl \cdot 2C_2H_5O_2N_2$ requires N, 16.8; Cl, 4.75%).

4- γ -Diethylaminopropylaminoquinoline (VI; R = H, R' = NH \cdot [CH $_2$] $_3$ ·NEt $_2$).—(a) 2-Chloro-4- γ -diethylaminopropylaminoquinoline in alcohol solution was shaken with hydrogen, Raney nickel, and potassium hydroxide (1 mol.), absorption of hydrogen ceasing when 1 mol. of hydrogen had been taken up. After filtration and evaporation to dryness the residue was treated with water and sodium hydroxide, and extracted with chloroform. Evaporation of the dried (K $_2$ CO $_3$) extract left an oil, purified by vacuum distillation, b. p. 171—172°/0.15 mm. (yield, 65%) (Found: N, 15.8. $C_{18}H_{22}N_2$ requires N, 16.3%), which crystallised on adding water to form a hydrate, m. p. 57° not depressed by an authentic specimen prepared according to method (b) (Found: C, 69.5; H, 8.6. $C_{18}H_{22}N_2 \cdot H_2O$ requires C, 69.8; H, 9.1%).

(b) 4-Chloroquinoline (1.95 g.), γ -diethylaminopropylamine (3 c.c.), and potassium iodide (0.05 g.) were stirred and heated at 180° for 8 hours. The resulting mixture after being cooled was extracted with 10% acetic acid containing sodium acetate (0.5 g.), and the extract treated with decolorising carbon, filtered, and made alkaline with sodium hydroxide. The product, isolated with ether, had b. p. 173—174°/0.15 mm. and gave the hydrate, m. p. 56°. It gave a dipicrate which crystallised from 2-ethoxyethanol-alcohol as pale yellow needles, m. p. 180—182° (Found: C, 47.2; H, 4.1; N, 18.0. $C_{18}H_{22}N_2 \cdot 2C_2H_5O_2N_2$ requires C, 47.0; H, 4.1; N, 17.6%).

2-Chloro-4- β -diethylaminoethylaminoquinoline (VI; R = Cl, R' = NH \cdot [CH $_2$] $_2$ ·NEt $_2$).—Prepared by careful addition of phosphoryl chloride to the dihydrate of the corresponding hydroxy-compound, followed by boiling for 18 hours and working up in the manner described for the corresponding γ -diethylaminopropylamino-derivative, this was obtained as a faintly yellow viscous oil, b. p. 183—184°/0.07 mm., which crystallised on addition of water to give the hydrate (yield, 36.6 g.) which crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 80—82° (Found: C, 60.9; H, 7.2; Cl, 11.6. $C_{18}H_{20}N_2Cl \cdot H_2O$ requires C, 60.9; H, 7.45; Cl, 12.0%).

4-Anilino-2-hydroxyquinoline (VII; R = H, R' = OH).—2:4-Dihydroxyquinoline (8.05 g.), aniline (23.3 g., 5 mols.), and aniline hydrochloride (6.5 g., 1 mol.) were stirred and heated at 180—190° for 12 hours. After removal of excess of aniline by steam distillation, the crystalline residue was collected and extracted with hot dilute sodium hydroxide and then washed, first with water, and then with hot methanol to remove a violet-coloured impurity. 4-Anilino-2-hydroxyquinoline remained as slightly bluish-grey prisms, m. p. 319—321° unchanged on crystallisation from 2-ethoxyethanol (v. Niementowski, *loc. cit.*, gives m. p. 318°; Dziewoński and Dymek, *loc. cit.*, give m. p. 316°) (Found: N, 12.1. Calc. for $C_{18}H_{13}ON_2$: N, 11.9%).

The same product was obtained in 87% yield by using boric acid in place of aniline hydrochloride and heating for 40 hours, but without an acid catalyst no product was formed.

4- p -Chloroanilino-2-hydroxyquinoline (VII; R = Cl, R' = OH).—2:4-Dihydroxyquinoline (40.25 g.), p -chloroaniline (160 g.), and p -chloroaniline hydrochloride (41.0 g.) were heated with stirring for 4 hours at 180—190°. While still warm, the mixture was stirred with warm methanol (150 c.c.), and the residue filtered off and washed with methanol until free from blue colour, to leave a colourless crystalline product. This was ground with hot water and then with dilute sodium hydroxide, filtered, washed with water, and dried (yield, 89%). It formed colourless crystals from 2-ethoxyethanol, m. p. 296—298° (Found: N, 10.6; Cl, 13.8. $C_{18}H_{11}ON_2Cl$ requires N, 10.35; Cl, 13.1%).

2-Chloro-4-anilinoquinoline (VII; R = H, R' = Cl).—4-Anilino-2-hydroxyquinoline (10.6 g.) and phosphoryl chloride (25 c.c.) were heated at 110—120° for 1½ hours and the solution was then evaporated under reduced pressure at 50—60°. The remaining greenish-yellow solid was ground under alcohol, and the mixture made alkaline with ammonia, diluted with water, filtered, washed, and dried. The chloro-compound (yield, 98%) had m. p. 162—164° unchanged after crystallisation from methanol from which it separated as thick colourless prisms (Found: N, 11.4; Cl, 13.9. Calc. for $C_{18}H_{11}N_2Cl$: N, 11.0; Cl, 13.9%). v. Niementowski (*loc. cit.*) gives m. p. 156°.

When the chloro-compound (1.28 g.) in alcohol (50 c.c.) was shaken with hydrogen in presence of Raney nickel and potassium hydroxide (0.3 g.), absorption of 1 mol. of hydrogen took place fairly rapidly. The mixture was then filtered and the solvent evaporated. Digestion of the solid residue with water gave a product which after crystallisation from methanol had m. p. 196—198° undepressed by an authentic specimen prepared from 4-chloroquinoline and aniline (Found: C, 81.5; H, 5.2; N, 12.8. Calc. for $C_{18}H_{11}N_2$: C, 81.8; H, 5.5; N, 12.7%).

2-Chloro-4-*p*-chloroanilinoquinoline (VII; $R = R' = Cl$), prepared in theoretical yield from 4-*p*-chloroanilino-2-hydroxyquinoline (58 g.) and phosphoryl chloride (150 c.c.) followed by working up in the manner described above for (VII; $R = H$, $R' = Cl$), had m. p. 174—175° unchanged by crystallisation from alcohol (Found: N, 9.4. $C_{15}H_{10}N_2Cl_2$ requires N, 9.7%).

4-*p*-Chloroanilino-2- β -diethylaminoethylaminoquinoline (II'; $R = Cl$, $R' = [CH_2]_2 \cdot NEt_2$).—2-Chloro-4-*p*-chloroanilinoquinoline (14.5 g.) and β -diethylaminoethylamine (9.0 g.) were heated at 130—140° for 14 hours. The mixture was dissolved in warm dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The extract was shaken with 5% acetic acid, the acetic acid extract made alkaline, and the product again extracted with chloroform. After drying (K_2CO_3), evaporation of the solvent left the base as an uncrystallisable oil which gave a gelatinous hydrochloride but a crystalline *dihydriodide* by evaporation of an alcoholic hydriodic acid solution of the base. This salt crystallised from alcohol in stout colourless prisms, softening from 240° and decomposing at 248° (Found: C, 39.8; H, 3.9. $C_{21}H_{25}N_4Cl \cdot 2HI$ requires C, 40.3; H, 4.3%) (3627).

4-*p*-Chloroanilino-2- γ -di-*n*-butylaminopropylaminoquinoline (II; $R = Cl$, $R' = [CH_2]_3 \cdot NBut_2$).—2-Chloro-4-*p*-chloroanilinoquinoline (9.35 g.), γ -di-*n*-butylaminopropylamine (10 g.), and powdered potassium iodide (0.1 g.) were heated and stirred at 150—160° for 6 hours. The resulting mixture was treated with warm sodium hydroxide, cooled, and extracted with chloroform. The residue left after evaporation of the chloroform was extracted with 5% acetic acid (200 c.c.), decanted from a little undissolved oil, and extracted with ether. The aqueous layer was made alkaline and extracted with chloroform. After removal of the chloroform from the dried extract, excess of amine was removed by heating to 200°/0.1 mm. and the residual base converted into its *dihydriodide* which was induced to crystallise by trituration with dilute alcohol and then recrystallised from methanol-ethyl acetate; m. p. 200—202° (Found: C, 45.1; H, 5.7; 1 mg. = 0.76 mg. AgX. $C_{26}H_{36}N_4Cl \cdot 2HI$ requires C, 45.0; H, 5.3; 1 mg. = 0.88 mg. AgX).

4-Chloro-2-arylaminoquinolines (VIII; $R' = Cl$).—A mixture of 2:4-dichloroquinoline (0.1 g.-mol.), the appropriate arylamine (0.1 g.-mol.), and acetic acid (40 c.c.) was stirred and heated on the steam-bath for times varying from $\frac{1}{2}$ hour to 2 hours. In some experiments (procedure *a*) fused sodium acetate was then added to neutralise the liberated hydrochloric acid and the mixture poured into water. In others (procedure *b*) the mixture was diluted with water to precipitate the hydrochloride which was then collected and boiled with methanolic ammonia followed by dilution with water. In either case, the precipitated base was collected when solid, dried, and crystallised to constant m. p. Table II gives details of the compounds prepared.

TABLE II.

4-Chloro-2-arylaminoquinolines (VIII; $R' = Cl$)

R.	Pro- cedure.	Yield (%).	Formula.	M. p.	Solvent.	Analysis.			
						Found (%).	Reqd. or calc. (%).		
H	<i>a</i>	53	$C_{15}H_{11}N_2Cl$	162—163° *	alcohol (rhombic prisms)	N. 10.6 Cl. 14.6	N. 11.0 Cl. 13.95		
Cl	<i>b</i>	50	$C_{15}H_{10}N_2Cl_2$	135—136	methanol (needles)	9.7 24.5	9.7 24.5		
MeO	<i>a</i>	43	$C_{16}H_{13}ON_2Cl$	140	alcohol (needles)	10.1 12.0	9.85 12.4		
Me	<i>a</i>	40	$C_{16}H_{13}N_2Cl$	115.5—116.5	methanol (stout prisms)	10.8 13.5	10.4 13.2		
NO ₂	<i>b</i>	43	$C_{15}H_{10}O_2N_2Cl$	263—265	dioxan (prisms)	13.7 12.0	14.0 11.85		
2- β -Naphthyl- amino-deriv- ative	<i>b</i>	34	$C_{19}H_{13}N_2Cl$	108—110	aq. methanol (needles and prisms)	9.8 11.7	9.2 11.65		
2-(6'-Bromo- β - naphthyl- amino)-deriv- ative	<i>b</i>	50	$C_{19}H_{12}N_2ClBr$	152—154	<i>n</i> -propanol	7.8 1 mg. = 0.853 mg. AgX	7.3 1 mg. = 0.864 mg. AgX		

* Dziewoński and Dymek, *Chem. Zentr.*, 1938, II, 1953, give m. p. 161°.

Reductive Dehalogenation of 4-Chloro-2-anilinoquinoline.—4-Chloro-2-anilinoquinoline (1.28 g.) and potassium hydroxide (0.3 g.) in alcohol (50 c.c.) were shaken with hydrogen and Raney nickel. Absorption of hydrogen was rapid and ceased after the theoretical uptake had occurred. The solution was filtered from catalyst and evaporated and water was added. The resulting oil soon solidified and was filtered off and dried. Crystallisation from dilute methanol and then from light petroleum (b. p. 60—80°) gave 2-anilinoquinoline as glistening colourless plates, m. p. 102—103° (Found: C, 81.4; H, 5.3; N, 13.0. Calc. for $C_{15}H_{11}N_2$: C, 81.8; H, 5.5; N, 12.7%).

2-*p*-Chloroanilino-4- γ -diethylaminopropylaminoquinoline (I; $R = Cl$, $R' = [CH_2]_3 \cdot NEt_2$).—(a) 2-Chloro-4- γ -diethylaminopropylaminoquinoline (8.1 g.), *p*-chloroaniline (10.65 g.), and powdered potassium iodide (0.1 g.) were heated at 200° for 6 hours with stirring. The mixture was dissolved in hot dilute hydrochloric acid and the filtered solution cooled and made alkaline with sodium hydroxide. The precipitated product was isolated with chloroform and partitioned between 5% acetic acid (100 c.c.) and ether. The aqueous layer was made alkaline with sodium hydroxide and the product again extracted

with chloroform. After drying (K_2CO_3), removal of the chloroform left an oil which rapidly solidified and then crystallised from benzene-light petroleum and finally from benzene giving the base as colourless fine needles, m. p. 154—156° (Found: C, 69.2; H, 7.0; N, 14.9; Cl, 9.3. $C_{22}H_{17}N_4Cl$ requires C, 69.0; H, 7.05; N, 14.6; Cl, 9.35%). It was converted into the *dihydrochloride* by dissolving in alcohol, adding hydrochloric acid until the solution was acid to Congo-red, evaporating to dryness under reduced pressure at 50—60°, and then evaporating with benzene-alcohol to remove the last traces of hydrochloric acid. The solid residue then crystallised from alcohol-ethyl acetate in colourless fine needles, which were hydrated and decomposed above 110° (Found: C, 54.0; H, 6.7; N, 11.4; Cl', 15.0. $C_{22}H_{17}N_4Cl \cdot 2HCl \cdot 2H_2O$ requires C, 53.7; H, 6.7; N, 11.4; Cl', 14.5%). This salt is readily soluble in water.

(b) 2-Chloro-4- γ -diethylaminopropylaminoquinoline (5.15 g.), *p*-chloroaniline (2.25 g.), water (20 c.c.), ethanol (5 c.c.), and 10N-hydrochloric acid (1.7 c.c.) were refluxed together for 48 hours. After cooling and addition of sodium acetate, a little unreacted *p*-chloroaniline was removed by ether extraction. Basification of the aqueous layer precipitated a solid which was filtered off, dried, and crystallised from benzene giving the same product as in (a), m. p. and mixed m. p. 155—156° (yield, 4.3 g.).

(c) 4-Chloro-2-*p*-chloroanilinoquinoline (20 g.), γ -diethylaminopropylamine (18.0 g.), and powdered potassium iodide (0.3 g.) were heated with stirring in an oil-bath at 180—190° for 16 hours. A solution of the mixture in warm dilute hydrochloric acid was made alkaline with sodium hydroxide and extracted with chloroform. The solvent was removed, the residue digested with warm 50% acetic acid (250 c.c.), and the filtered solution basified and extracted with chloroform. After drying (K_2CO_3) and removal of the chloroform an oil was obtained which quickly solidified and was then crystallised from benzene (yield, 17.6 g.); it had m. p. 153—155°, and was identical with the compound made by methods (a) and (b) (Found: C, 68.6; H, 7.1%).

Using method (c) a number of other 2-arylamino-4-dialkylaminoalkylaminoquinolines were prepared. Details are given in Table III.

2 : 4-Dichloro-7 : 8-benzoquinoline.—2 : 4-Dihydroxy-7 : 8-benzoquinoline (78 g.) (prepared from α -naphthylamine and ethyl malonate, cf. E.P. 332911 and Baumgarten and Kärger, *Ber.*, 1927, 60, 832) and phosphoryl chloride (200 c.c.) were heated at 90—100° for $\frac{1}{2}$ hour during which time hydrogen chloride was copiously evolved. The temperature was then raised to 120—125° and maintained for 3 $\frac{1}{2}$ hours. The resulting clear solution was cooled and added to crushed ice with stirring. The precipitated product was filtered off, washed free from acid, dried, and refluxed with acetone (1 l.). After filtration from insoluble matter, the acetone was distilled off and the residue crystallised from ethyl acetate (yield, 48.5 g.). 2 : 4-Dichloro-7 : 8-benzoquinoline formed long colourless needles from acetone, m. p. 134—135° (Found: C, 63.0; H, 3.5; Cl, 28.3. $C_{18}H_7NCl_2$ requires C, 62.9; H, 2.8; Cl, 28.6%).

4-Chloro-2-*p*-chloroanilino-7 : 8-benzoquinoline.—2 : 4-Dichloro-7 : 8-benzoquinoline (24.8 g.), *p*-chloroaniline (12.7 g.), *p*-chloroaniline hydrochloride (0.1 g.), and 2-ethoxyethanol (30 c.c.) were heated in an oil-bath at 160° for 3.5 hours. The mixture was then cooled and diluted with water, and the precipitated product filtered off and dissolved in boiling alcohol (350 c.c.) with the addition of sufficient ammonia to give an alkaline reaction. The resulting solution was treated with an equal volume of water. The product, when solid, was collected, dried, and crystallised first from benzene and then from butanol (yield, 40%) giving needles, m. p. 160—162° (Found: Cl, 20.4. $C_{21}H_{15}N_2Cl_2$ requires Cl, 20.4%).

2-*p*-Chloroanilino-4- γ -diethylaminopropylamino-7 : 8-benzoquinoline.—The preceding chloro-compound (17.6 g.), γ -diethylaminopropylamine (13.5 g.), and powdered potassium iodide (0.3 g.) were heated at 175—185° with stirring for 24 hours. Worked up in the usual way for this type of compound the base was obtained as a glass which could not be induced to crystallise. It was therefore dissolved in hot acetone (100 c.c.), and hydrochloric acid added until the solution showed acidity to Congo-red. On cooling, the *dihydrochloride* crystallised out as a hydrate and was recrystallised from acetone-water, m. p. 108—110° (Found: C, 55.3; H, 6.4; N, 10.0; Cl', 13.6. $C_{22}H_{17}N_4Cl \cdot 2HCl \cdot 3H_2O$ requires C, 55.8; H, 6.3; N, 10.0; Cl', 12.7%).

7-Chloro-2 : 4-dihydroxyquinoline.*—This was prepared by a modification of a method for 2 : 4-dihydroxyquinoline described by Koller (*Ber.*, 1927, 60, 1108). Methyl 4-chloroanthranilate (100 g.) (Hunn, *J. Amer. Chem. Soc.*, 1923, 45, 1028), ethyl malonate (86.2 g.), and sodium methoxide (29 g.) were mixed in a flask fitted with a condenser arranged for distillation. After the mixture had been stirred at 70° until homogeneous (ca. 1 hour), the temperature was raised slowly to 140—150° and then maintained for 6 hours. Alcohol distilled and the mixture thickened, eventually becoming quite solid. After cooling, the mixture was repeatedly extracted with cold dilute sodium hydroxide and the extracts were acidified to precipitate what was probably methyl 7-chloro-2 : 4-dihydroxyquinoline-3-carboxylate (89 g.). This ester (35 g.) was hydrolysed and decarboxylated by heating on the steam-bath overnight with sodium hydroxide (13 g. in 350 c.c. water); after being filtered from a little insoluble material the filtrate was acidified. The precipitate was collected, washed, and boiled with dilute sodium carbonate solution, and the solution cooled, filtered, and acidified. 7-Chloro-2 : 4-dihydroxyquinoline was precipitated as an almost colourless powder, m. p. 332—340° (decomp.) (Found: N, 6.7; Cl, 18.5. Calc. for $C_9H_4O_2NCl$: N, 7.2; Cl, 18.2%). This substance has been prepared very recently by another modification of Koller's method by Lutz *et al.* (*J. Amer. Chem. Soc.*, 1946, 68, 1285).

7-Chloro-4- γ -diethylaminopropylamino-2-hydroxyquinoline.*—7-Chloro-2 : 4-dihydroxyquinoline (30 g.) and γ -diethylaminopropylamine (41.2 g.) were heated at 170—180° for 20 hours and then worked up as described for 4- γ -diethylaminopropylamino-2-hydroxyquinoline to give the compound as practically colourless needles, m. p. 228—229° (Found: C, 62.2; H, 6.9; N, 13.9; Cl, 12.0. $C_{18}H_{12}ON_2Cl$ requires C, 62.4; H, 7.1; N, 13.7; Cl, 11.55%).

2 : 7-Dichloro-4- γ -diethylaminopropylaminoquinoline.*—The above hydroxy-compound (12 g.) and phosphoryl chloride (24 c.c.) were heated by means of an oil-bath at 130—140° for 16 hours followed by working up in the usual way for this type of compound to give the product, m. p. 82—87°, characterised as

* Experiments by Mrs. J. M. Wilson.

TABLE III.
2-Arylamino-4-aminoalkylaminoquinolines.

Substituent at 2.	Substituent at 4.	Derivative.	M. p. mm.	Solvent; crystalline form.	Formula.	Analysis.							
						Found (%).				Required (%).			
						C.	H.	N.	Cl.	C.	H.	N.	Cl.
<i>p</i> -Chloroanilino	NH·[CH ₂] ₂ ·NEt ₂	—	B. p. 253°/0.1 mm.	Very viscous oil	—	—	—	—	—	—	—	—	—
		Dihydrochloride	169—171° (decomp.)	Alcohol-ethyl acetate; needles	C ₂₁ H ₂₅ N ₃ Cl ₂ ·2HCl, H ₂ O	55.3	6.3	—	15.6	54.9	6.3	—	15.45
		Dihydroiodide	253—254° (decomp.)	Alcohol-ethyl acetate; prisms	C ₂₁ H ₂₅ N ₃ Cl ₂ ·2HI	40.1	4.4	—	—	40.3	4.3	—	—
		Dihydrochloride	201—203° (decomp.)	Alcohol-ethyl acetate; needles	C ₂₃ H ₂₉ N ₃ Cl ₂ ·2HCl, H ₂ O	56.8	6.4	11.8	14.9	56.6	6.8	11.5	14.6
<i>p</i> -Chloroanilino	NH·[CH ₂] ₄ ·NEt ₂												
<i>p</i> -Chloroanilino	NH·CHMe·[CH ₂] ₃ ·NEt ₂ ¹	Dipicrate	230—232° (decomp.)	2-Ethoxyethanol-pyridine; yellow needles	C ₂₄ H ₃₁ N ₄ Cl ₂ ·2C ₄ H ₃ O ₇ N ₃	49.1	4.5	16.6	—	49.7	4.3	16.1	—
<i>p</i> -Chloroanilino	* NH·[CH ₂] ₂ ·NMe ₂	Dihydrochloride	86—88° (decomp.)	Alcohol-ethyl acetate	C ₂₀ H ₂₃ N ₄ Cl ₂ ·2HCl, 1.5H ₂ O	52.9	6.3	12.2	15.0	52.8	6.2	12.3	15.6
<i>p</i> -Chloroanilino	* NH·[CH ₂] ₃ ·N < [CH ₂] ₄ > CH ₂	Dihydrochloride	86—88°	Dilute hydrochloric acid	C ₂₃ H ₂₇ N ₄ Cl ₂ ·2HCl, 5H ₂ O	49.6	6.8	10.6	13.1	49.5	7.0	10.05	12.8
<i>p</i> -Anisidino	NH·[CH ₂] ₂ ·NEt ₂	Dihydroiodide	146—148° (decomp.)	Aqueous alcohol; needles	C ₂₂ H ₂₅ ON ₄ ·2HI, H ₂ O	41.7	5.1	—	—	41.4	5.0	—	—
<i>p</i> -Toluidino	NH·[CH ₂] ₂ ·NEt ₂	—	109—111°	<i>cyclo</i> Hexane; prisms	C ₂₂ H ₂₈ N ₄ ·0.5H ₂ O	74.4	7.8	16.0	—	74.0	8.1	15.7	—
<i>p</i> -Nitroanilino	NH·[CH ₂] ₂ ·NEt ₂	Dihydrochloride	182—184° (softening at 172°)	Alcohol-ethyl acetate	C ₂₂ H ₂₇ O ₂ N ₄ ·2HCl, 4H ₂ O	49.2	6.0	13.7	—	49.1	6.8	13.0	—
<i>β</i> -Naphthyl-amino	NH·[CH ₂] ₂ ·NEt ₂	Dihydroiodide	127—128°	Methanol	C ₂₈ H ₂₉ N ₄ ·2HI, H ₂ O	45.6	5.0	—	—	45.6	5.0	—	—
6-Bromo- <i>β</i> -naphthyl-amino	NH·[CH ₂] ₃ ·NEt ₂	—	149—150°	Benzene-light petroleum	C ₂₈ H ₂₉ N ₄ Br	65.9	5.8	11.8	—	65.4	6.1	11.7	—

¹ For biological test the picrate was dissolved in pyridine, the solution added to aqueous sodium hydroxide, and the base extracted with ether which was then thoroughly washed with sodium hydroxide and water, dried, and evaporated, giving the base as an oil. This was made soluble with lactic acid.

its *dipicrate* which crystallised from aqueous 2-ethoxyethanol and had m. p. 194—195° (Found : N, 15.8; Cl, 9.5. $C_{18}H_{21}N_3Cl_2 \cdot 2C_6H_5O_2N_3$ requires N, 16.1; Cl, 9.1%).

7-Chloro-2-p-chloroanilino-4-γ-diethylaminopropylaminoquinoline.—2 : 7-Dichloro-4-γ-diethylaminopropylaminoquinoline (8.96 g.), *p*-chloroaniline (10.6 g.), and potassium iodide (0.1 g.) were heated for 8 hours at 200°. The mixture was treated with hot dilute hydrochloric acid, made alkaline with sodium hydroxide, and steam distilled to remove unchanged *p*-chloroaniline. The residual oil was separated and dissolved in 5% acetic acid, and the solution extracted with ether. Basification followed by isolation with chloroform then gave the *product* which crystallised from benzene-light petroleum as colourless laminae, m. p. 144—145° (Found : C, 63.0; H, 6.1; N, 13.7; Cl, 17.1. $C_{23}H_{28}N_4Cl_2$ requires C, 63.3; H, 6.2; N, 13.4; Cl, 17.1%).

2 : 4-Dihydroxy-3-methylquinoline.—Aniline (46.5 g.) and ethyl methylmalonate (87 g.), contained in a flask fitted with a long condenser allowing only the liberated alcohol to escape, were heated at 230—240° for $\frac{1}{2}$ hour, then at 290—300° for $1\frac{1}{2}$ hours, and finally raised to 340° during $\frac{1}{2}$ hour. The cooled mass was boiled with acetone (100 c.c.) for 10 hours and the insoluble material filtered off after cooling. It was then boiled with sodium carbonate solution (700 c.c. of 10%) for 10 minutes and cooled, and the solution was filtered and the product precipitated with hydrochloric acid (yield, 53%). Crystallised from 2-ethoxyethanol and then from butanol it formed almost colourless prisms, m. p. 265—268° (decomp.) (Found : C, 68.3; H, 4.9; N, 8.4. Calc. for $C_{10}H_9O_2N$: C, 68.6; H, 5.1; N, 8.0%) (Gabriel and Gerhard, *Ber.*, 1921, 54, 1067, give m. p. > 270°).

2 : 4-Dichloro-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (25 g.) and phosphoryl chloride (75 c.c.) were heated at 100—110° for $\frac{1}{2}$ hour and then at 120—125° for 5 hours. The mixture was then cooled and poured on ice. The precipitated product was filtered off, washed free from acid with water, dried (yield, 29.7 g.), and crystallised from 80% alcohol, m. p. 90—91° (Found : Cl, 33.1. Calc. for $C_{10}H_7NCl_2$: Cl, 33.5%) (Gabriel and Gerhard, *loc. cit.*, give m. p. 83—84°).

4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (20 g.) and γ-diethylaminopropylamine (30 g.) were heated at 180—190° for 22.5 hours and the mixture was cooled and poured into water. The *product*, precipitated as an oil, soon solidified. It was collected, dissolved in 5% acetic acid, precipitated with ammonia, and dried at 60° (yield, 47.5%). It crystallised from aqueous alcohol as pale yellow stout prisms, m. p. 105—106° (Found : N, 14.7. $C_{17}H_{25}ON_3$ requires N, 14.6%).

4-γ-Diethylaminopropylamino-2-hydroxy-3-ethylquinoline, prepared in exactly the same manner from 2 : 4-dihydroxy-3-ethylquinoline (Baumgarten and Kargel, *loc. cit.*) and γ-diethylaminopropylamine, crystallised from aqueous alcohol; m. p. 100—101° (Found : N, 14.2. $C_{18}H_{27}ON_3$ requires N, 14.0%).

2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline.—4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline (13.35 g.) and phosphoryl chloride (30 c.c.) were heated at 115—125° for 18 hours. Most of the excess of phosphoryl chloride was then removed under diminished pressure and the residue dissolved in water, made alkaline with potassium hydroxide, and extracted with ether. The dried ethereal extract was evaporated and the residual oil extracted with cold light petroleum (b. p. 40—60°) (100 c.c.), filtered, and evaporated. 2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline remained as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol-alcohol as fine yellow needles of indefinite melting point (ca. 160°) (Found : N, 16.6; Cl, 4.7. $C_{17}H_{24}N_3Cl \cdot 2C_6H_5O_2N_3$ requires N, 16.5; Cl, 4.65%).

4-Chloro-2-p-chloroanilino-3-methylquinoline.—2 : 4-Dichloro-3-methylquinoline (21.2 g.) and *p*-chloroaniline (12.75 g.) in acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring. Crystalline material was deposited during the reaction. This was collected after dilution with water, washed, and stirred overnight with methanol containing excess of ammonia. Water was then added, and the product collected, washed, and dried. This crude material was ground and extracted with cold dioxan leaving undissolved 2 : 4-di-*p*-chloroanilino-3-methylquinoline (3.1 g.), m. p. 266—268° (Found : Cl, 18.0. $C_{22}H_{17}N_3Cl_2$ requires Cl, 18.0%). The dioxan filtrate from this di-condensation product was diluted with water and the precipitated material, initially an oil which gradually solidified, filtered off and crystallised from alcohol, giving 4-chloro-2-p-chloroanilino-3-methylquinoline as colourless fine needles, m. p. 120—121° (Found : N, 9.3; Cl, 22.9. $C_{16}H_{12}N_3Cl_2$ requires N, 9.25; Cl, 23.4%) (yield, 15.85 g.).

2-p-Chloroanilino-4-γ-diethylaminopropylamino-3-methylquinoline.—(a) Crude 2-chloro-4-γ-diethylaminopropylamino-3-methylquinoline (9.65 g.), *p*-chloroaniline (12.1 g.), and potassium iodide (0.1 g.) were heated at 200° for 12 hours. The mass was dissolved in alcohol, and the solution made alkaline with sodium hydroxide and steam distilled. The residual oil was isolated with chloroform and shaken with 5% acetic acid (150 c.c.) and ether. The aqueous layer was separated and re-extracted with ether, and then made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract left the base as an oil which could not be induced to crystallise. The picrate and hydrochloride likewise failed to crystallise. A solution of the base in dilute hydrochloric acid on treatment with perchloric acid gave the *perchlorate* which crystallised from alcohol in rosettes of colourless needles, m. p. 216—218° (Found : C, 46.1; H, 4.9; N, 9.7. $C_{23}H_{28}N_4Cl_2 \cdot 2HClO_4$ requires C, 46.2; H, 5.2; N, 9.4%).

(b) 4-Chloro-2-p-chloroanilino-3-methylquinoline (10 g.), γ-diethylaminopropylamine (8.6 g.), and potassium iodide (0.15 g.) were heated under reflux in an oil-bath at 190—200° for 22 hours. When cool, the semi-solid mass was treated with aqueous sodium hydroxide and extracted with chloroform. After evaporation of the solvent the residue was stirred with 5% acetic acid (150 c.c.), filtered and extracted with ether. The acetic solution was then basified and extracted with chloroform. Evaporation of the dried chloroform extract left an oily base contaminated with γ-diethylaminopropylamine. This was removed by heating overnight at 120—130°/15 mm. and the residue dissolved in dilute hydrochloric acid and treated with perchloric acid to give the same perchlorate as in (a), m. p. and mixed m. p. 215—217° (Found : C, 45.7; H, 5.2%).

For biological testing the perchlorates from (a) and (b) were combined and treated with aqueous sodium hydroxide, and the liberated base was isolated with chloroform.

2-Chloro-4- γ -diethylaminopropylamino-3-ethylquinoline.—4- γ -Diethylaminopropylamino-2-hydroxy-3-ethylquinoline (15 g.) and phosphoryl chloride (35 c.c.) were heated at 115–125° for 16 hours followed by working up as described for the corresponding 3-methyl compound to give the product as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as yellow plates, m. p. 144–146° (Found: N, 16.3; Cl, 4.6. $C_{18}H_{22}N_2Cl_2 \cdot 2C_4H_8O_2 \cdot N_2$ requires N, 16.2; Cl, 4.6%).

2:4-Dichloro-3-ethylquinoline.—2:4-Dihydroxy-3-ethylquinoline (50 g.) and phosphoryl chloride (150 c.c.) were heated with stirring at 100–110° for $\frac{1}{2}$ hour and then at 120–125° for 4 hours. The cooled mixture was poured on ice and after being stirred for several hours the product was extracted with ether. Evaporation of the washed and dried ethereal extract gave an oil which was purified by vacuum distillation, b. p. 182–184°/21 mm. (yield, 88%) (Found: Cl, 31.0. $C_{11}H_8NCl_2$ requires Cl, 31.4%).

4-Chloro-2-p-chloroanilino-3-ethylquinoline.—2:4-Dichloro-3-ethylquinoline (22.6 g.), *p*-chloroaniline (12.75 g.), and acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring and then refluxed for 10 minutes. When cold, the mixture was diluted with water and made strongly acid to Congo-red with hydrochloric acid. The practically colourless crystalline powder thereby obtained was filtered off, washed with water, and heated on the steam-bath for 10 minutes with methanol (100 c.c.) and sufficient ammonia to give an alkaline reaction. Dilution with water gave a product which was filtered off, dried, and crystallised from alcohol; it was obviously a mixture (18.4 g.). Crystallisation from dioxan (40 c.c.) gave fine needles of 2:4-di-*p*-chloroanilino-3-ethylquinoline (3.6 g.), m. p. 224–226° (Found: Cl, 17.3. $C_{22}H_{18}N_2Cl_2$ requires Cl, 17.4%), and dilution with water the required 4-chloro-2-p-chloroanilino-3-ethylquinoline which crystallised from alcohol in stout prisms, m. p. 132–133° (Found: N, 9.0; Cl, 22.4. $C_{11}H_8N_2Cl_2$ requires N, 8.8; Cl, 22.4%).

2-Amino-4- γ -diethylaminopropylaminoquinoline (VI; R = NH₂, R' = NH·[CH₂]₃·NET₂).—Ammonia was passed through a solution of 2-chloro-4- γ -diethylaminopropylaminoquinoline (5.2 g.) in phenol (20 g.) at 170–180° for 18 hours. The cooled mixture was treated with aqueous sodium hydroxide and ether, and the ether layer washed thoroughly with dilute sodium hydroxide and then with water and dried (Na₂SO₄). Removal of the solvent left a syrup which solidified on trituration with light petroleum (b. p. 60–80°). By crystallisation from benzene–light petroleum the amino-compound was obtained as colourless stout prisms, m. p. 125–126° (Found: N, 20.0. $C_{16}H_{22}N_4$ requires N, 20.6%).

2-p-Chlorophenylthioureido-4- γ -diethylaminopropylaminoquinoline (X; R = [CH₂]₃·NET₂).—2-Amino-4- γ -diethylaminopropylaminoquinoline (13.5 g.), *p*-chlorophenyl isothiocyanate (9.0 g.), and dry xylene (30 c.c.) were refluxed for 1 hour. On cooling, the clear solution deposited crystals which were filtered off, washed with benzene, and dried. Crystallisation from xylene gave pale yellow stout prisms (yield, 72%), m. p. 188–189° (Found: N, 15.4; S, 6.9. $C_{22}H_{22}N_4ClS$ requires N, 15.9; S, 7.25%).

2-p-Chlorophenylguanidino-4- γ -diethylaminopropylaminoquinoline (XI; R = [CH₂]₃·NET₂).—The above thioureido-compound (6.5 g.) was stirred with saturated alcoholic ammonia (100 c.c.) and mercuric oxide (7 g.) for 24 hours at 30–35° with the continuous passage of ammonia into the solution. After cooling, the mixture was filtered and the dried residue extracted with hot xylene from which the product separated on cooling (yield, 78%). It formed colourless needles from xylene, m. p. 208° (Found: C, 65.3; H, 6.5; N, 19.8. $C_{23}H_{26}N_6Cl$ requires C, 65.0; H, 6.8; N, 19.8%). 2-p-Chlorophenylguanidino-4- γ -diethylaminopropylaminoquinoline is only very sparingly soluble in alcohol.

2-Amino-4- β -diethylaminoethylaminoquinoline (VI; R = NH₂, R' = NH·[CH₂]₂·NET₂).—Ammonia was passed for 22 hours into a solution of 2-chloro-4- β -diethylaminoethylaminoquinoline (21.9 g.) in phenol (50 g.) at 170–180°. The mixture was cooled, treated with sodium hydroxide solution, and shaken with ether. The ether solution after being washed with sodium hydroxide and then with water was extracted with 5% acetic acid. Addition of ammonia to this extract to render it alkaline to Brilliant-yellow precipitated 4- β -diethylaminoethylamino-2-phenoxyquinoline (VI; R = OPh, R' = NH·[CH₂]₂·NET₂) as an oil which rapidly solidified. After being collected and dried, it crystallised from cyclohexane in large irregular prisms, m. p. 104–105° (Found: N, 12.9. $C_{21}H_{25}ON_3$ requires N, 12.5%). Addition of sodium hydroxide to the aqueous filtrate precipitated 2-amino-4- β -diethylaminoethylaminoquinoline as an oil which gradually solidified (yield, 13 g.). After drying, it crystallised from cyclohexane with the addition of a little water as practically colourless laminae, m. p. 114–115° (Found: C, 69.8; H, 8.7; N, 21.8. $C_{15}H_{22}N_4$ requires C, 69.75; H, 8.5; N, 21.75%). Under the above conditions of crystallisation it was sometimes obtained as a *hydrate*, m. p. 75–77° (Found: C, 63.2; H, 8.8; N, 18.9. $C_{15}H_{22}N_4 \cdot 1.5H_2O$ requires C, 63.2; H, 8.8; N, 19.6%).

2-p-Chlorophenylthioureido-4- β -diethylaminoethylaminoquinoline (X; R = [CH₂]₂·NET₂).—The preceding thiourea (6 g.) and mercuric oxide (6 g.) were added to saturated alcoholic ammonia (100 c.c.) at 0°. With stirring, the mixture was allowed to regain room temperature, then warmed to 30–35° and ammonia passed in for 2 hours. After being stirred at this temperature for 19 hours the mixture was filtered and the insoluble residue dried and extracted with benzene to give the *product* as colourless needles, m. p. 202–203° (Found: N, 20.2. $C_{22}H_{27}N_6Cl$ requires N, 20.5%).

2-p-Chlorophenylguanidino-4- β -diethylaminoethylaminoquinoline (XI; R = [CH₂]₂·NET₂).—The preceding thiourea (6 g.) and mercuric oxide (6 g.) were added to saturated alcoholic ammonia (100 c.c.) at 0°. With stirring, the mixture was allowed to regain room temperature, then warmed to 30–35° and ammonia passed in for 2 hours. After being stirred at this temperature for 19 hours the mixture was filtered and the insoluble residue dried and extracted with benzene to give the *product* as colourless needles, m. p. 202–203° (Found: N, 20.2. $C_{22}H_{27}N_6Cl$ requires N, 20.5%).

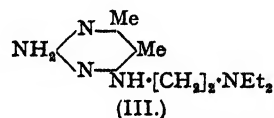
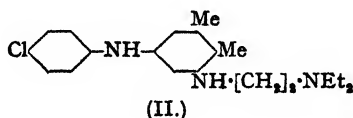
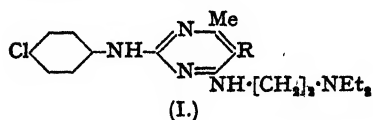
168. Synthetic Antimalarials. Part XVIII. 3-Dialkylaminoalkyl-aminodiphenylamines.

By FREDERICK G. MANN and J. W. GEOFFREY PORTER.

In order to determine whether the antimalarial activity of certain 2-anilino-4-dialkylamino-alkylaminopyrimidines of type (I) was determined primarily by their general structure, the corresponding compounds in which the pyrimidine ring has been replaced by a benzene ring, *i.e.*, diphenylamines of type (II), have been synthesised. The similar benzene analogues of the active 2-amino-4-dialkylaminoalkylaminopyrimidines of type (III) have also been synthesised.

All these benzene analogues proved to be devoid of antimalarial activity, however, and the activity of both the above types of pyrimidine compound must therefore be intimately associated either with the pyrimidine ring itself or with the tautomerism which this ring allows.

When this investigation was started, it was known that 2-*p*-chloroanilino-4- β -diethylamino-ethylamino-6-methylpyrimidine (I, R = H) showed marked antimalarial activity against avian malaria; the corresponding *p*-methoxyanilino-compound showed lower activity, but the 5:6-dimethyl homologue (I, R = Me) an activity slightly greater than that of (I, R = H) (Curd and Rose, *J.*, 1945, 343; Curd, Richardson, and Rose, *ibid.*, p. 378). Many other homologues, having similar 4-dialkylaminoalkylamino-substituents, also showed varying degrees of activity.



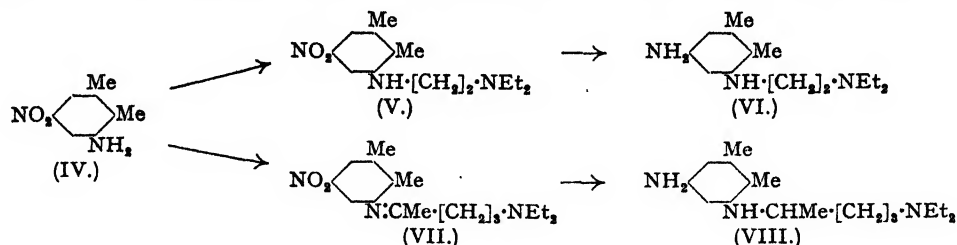
It had been suggested (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, 39, 157; Curd, Davis, and Rose, *J.*, 1946, 351) that these various anilino-pyrimidines might owe their antimalarial activity to their interference with some essential metabolic process involving riboflavin, due to the structural similarity which not only exists between riboflavin and the pyrimidines themselves, but might also exist between riboflavin and the most probable degradation products of these pyrimidines, for example, the corresponding 4-hydroxy-pyrimidines which could be formed by hydrolytic removal of the alkylamino-group from the drug. It was shown later by Madinaveitia (*Biochem. J.*, in the press) that the growth-inhibitory action of the above pyrimidines, as well as that of mepacrine and quinine, for *Lactobacillus casei* was actually antagonised by riboflavin.

It became of interest therefore to prepare diphenylamine compounds of type (II), which differed from compounds of type (I) only in that the pyrimidine ring of the latter had now been replaced by a benzene ring. If antimalarial activity is due primarily to a general structural similarity between riboflavin and the drug, compounds of type (II) should have an activity of the same order as that of their analogues of type (I); if, however, it is due primarily to a structural similarity between riboflavin and the main degradation products of the drug, then compounds of type (II), by virtue of their greater stability, might well prove inactive.

It should be noted, however, that a further factor enters here which might itself largely offset the result of any general structural similarity between the two classes of drugs. Pyrimidines of type (I) can clearly exist in several tautomeric forms (formulated in Part VIII, *J.*, 1946, 713), whereas in the benzene analogues of type (II) no such tautomerism can occur. It is noteworthy that a similar tautomerism can occur in mepacrine, and Schönhöfer (*Z. physiol. Chem.*, 1942, 274, 1) has suggested that the antimalarial activity of mepacrine is closely associated with this tautomerism.

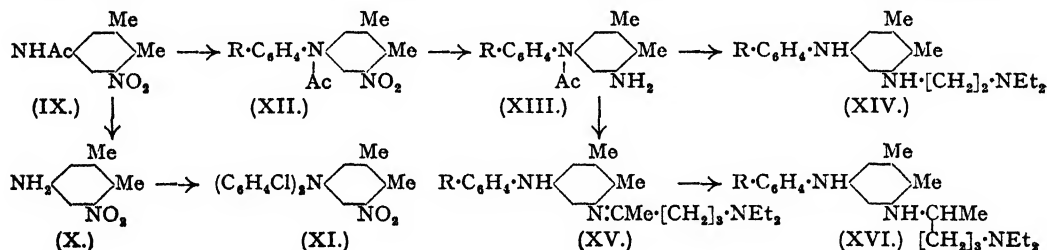
It is clear, however, that even if this structural-similarity factor is the underlying cause of the antimalarial activity of certain types of drug, it cannot apply to all types. For example, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1945, 357) have shown that 2-amino-4- β -diethylaminoethylamino-5:6-dimethylpyrimidine (III), which does not show this structural similarity with riboflavin, has an activity of approximately the same value as that of (I, R = Me). It is significant that Madinaveitia (*loc. cit.*) has found that the action of pyrimidines of type (III) is not antagonised by riboflavin. The additional object of the present investigation therefore was to prepare the benzene analogues of (III), in order to determine whether in this class of drug also the pyrimidine ring, with its accompanying tautomerism, was essential for antimalarial activity. The synthesis of these simpler monocyclic compounds is conveniently described before that of the more complex diphenylamine derivatives.

Condensation of 5-nitro-3-amino-*o*-xylene (IV) with β -diethylaminoethyl chloride furnished the hydrochloride of 5-nitro-3- β -diethylaminoethylamino-*o*-xylene (V). Catalytic reduction followed by basification then gave 5-amino-3- β -diethylaminoethylamino-*o*-xylene (VI). Many



attempts were then made to condense the amine (IV) with δ -bromo- α -diethylamino-*n*-pentane, $\text{CHMeBr} \cdot [\text{CH}_2]_3 \cdot \text{NEt}_2$, in order ultimately to make (VIII), *i.e.*, the analogue of (VI) containing the basic side chain of mepacrine. All such attempts failed, however, in spite of a variety of conditions employed. Ultimately success was achieved by utilising the method developed by Ashley and Grove (*J.*, 1945, 768) for introducing this side chain into the aminopyridines. For this purpose, methyl 3-diethylamino-*n*-propyl ketone was converted into the diethyl ketal, $\text{CMe}(\text{OEt})_2 \cdot [\text{CH}_2]_3 \cdot \text{NEt}_2$, which was readily condensed with the amine (IV) to give the anil (VII). This compound on catalytic reduction furnished 5-amino-3- δ -diethylamino- α -methyl-*n*-butylamino-*o*-xylene (VIII).

For the preparation of the corresponding diphenylamines, 4-amino-*o*-xylene was acetylated and then nitrated to furnish 3-nitro-5-acetamido-*o*-xylene (IX) (*cf.* Crossley and Morrell, *J.*, 1911, 99, 2350), hydrolysis then giving 3-nitro-5-amino-*o*-xylene (X). This amine was subjected to an Ullmann condensation with *p*-chloriodobenzene in the presence of copper, but



in spite of a wide variety of conditions the main product isolated was always 4':4''-dichloro-3-nitro-4:5-dimethyltriphenylamine (XI), and it was clear that the initial production of the diphenylamine must have been a slow process compared with its conversion into the triphenylamine derivative. It should be noted that this preferential formation of a tertiary amine by the Ullmann reaction is rare but not unique: Wibaut and La Bastide (*Rec. Trav. chim.*, 1933, 52, 493) have shown that 2-iodopyridine and 2-aminopyridine, when heated with potassium carbonate and copper, furnish the tri-2-pyridylamine.

This difficulty was overcome by employing the acetamido-compound (IX), which in the presence of copper bronze and potassium iodide readily combined with *p*-chloriodobenzene to form 4'-chloro-3-nitro-*N*-aceto-4:5-dimethyldiphenylamine (XII, $\text{R} = \text{p-Cl}$). The latter was then reduced to the 3-amino-derivative (XIII, $\text{R} = \text{Cl}$) which, after condensation with β -2-diethylaminoethyl chloride and subsequent hydrolysis, furnished 4'-chloro-3- β -diethylaminoethylamino-4:5-dimethyldiphenylamine (XIV, $\text{R} = \text{Cl}$).

When the acetyl group in (XIII) was removed, the resulting amine readily condensed with the above diethyl ketal to give the anil (XV, $\text{R} = \text{Cl}$), which on catalytic reduction gave 4'-chloro-3-(δ -diethylaminoethylamino)-4:5-dimethyldiphenylamine (XVI, $\text{R} = \text{Cl}$).

Attempts were then made to prepare compounds of type (XIV) and (XVI) in which $\text{R} = \text{p-MeO}$, as this group has considerable significance in many antimalarial compounds. *p*-Bromoanisole was successfully condensed with the acetamido-compound (IX), but the acetodiphenylamide could not readily be isolated: consequently the crude product was hydrolysed and the pure 3-nitro-4'-methoxy-4:5-dimethyldiphenylamine thus obtained. This compound was reduced to the 3-amino-derivative, which condensed with β -diethylaminoethyl chloride to give 3- β -diethylaminoethylamino-4'-methoxy-4:5-dimethyldiphenylamine (XIV,

R = MeO). The 3-amino-derivative also gave the anil (XV, R = MeO) which on hydrogenation furnished 3-*β*-diethylamino- α -methyl-*n*-butylamino-4'-methoxy-4 : 5-dimethyldiphenylamine (XVI, R = MeO). It should be noted that, whereas the constitution of the last compound is beyond doubt, that of (XIV, R = MeO) is not absolutely certain, since the ethyl chloride might conceivably condense with the secondary amino-group : the reactivity of the 3-amino-group is so very much greater, however, that this possibility can be ignored.

The two xylene derivatives (VI) and (VIII) and the four diphenylamine derivatives (XIV, R = Cl and MeO) and (XVI, R = Cl and MeO) have been tested against *P. gallinaceum* in chicks and found to be inactive not only against the blood forms but also prophylactically. It is clear, therefore, that the marked antimalarial activity of the two types of pyrimidine derivative (I) and (III) must be intimately associated either with the pyrimidine ring as such, or with the tautomerism which this ring allows, and that a superficial structural similarity with riboflavin which ignores this tautomerism, as in the diphenylamine derivatives, is insufficient to produce activity.

EXPERIMENTAL.

5-Nitro-3-amino-*o*-xylene (IV). This compound, prepared according to Noeltling, Braun, and Thesmar (*Ber.*, 1901, 34, 2242), was obtained in 35% yield as yellow needles, m. p. 111–112°.

5-Nitro-3- β -diethylaminoethylamino-*o*-xylene (V).—A solution of 5-nitro-3-amino-*o*-xylene (12 g.) in xylene (50 c.c.) was refluxed with 2-diethylaminoethyl chloride (45 c.c. of a 30% xylene solution; 1.1 mols.) for 4 hours. On cooling, the product, which had separated during the heating, solidified; it was collected, and recrystallised from ethyl alcohol-petrol (equal vols., 400 c.c.), furnishing pale yellow plates of the hydrochloride of the diethylamino-compound (V), m. p. 182–183° (Found : C, 55.8; H, 8.1. $C_{14}H_{20}O_2N_3 \cdot HCl$ requires C, 55.7; H, 8.0%) (15 g., 70%). This compound formed a *picrate*, yellow needles from aqueous acetone containing a slight excess of picric acid, m. p. 164–165° (Found : C, 48.3; H, 5.5. $C_{14}H_{20}O_2N_3 \cdot C_6H_3O_7N_3$ requires C, 48.5; H, 5.3%).

5-Amino-3- β -diethylaminoethylamino-*o*-xylene (VI) (6048).—A solution of the above hydrochloride (9 g.) in 95% ethyl alcohol (150 c.c.) was rapidly hydrogenated in the presence of Adams's platinum catalyst (0.2 g.) at room temperature and pressure. The filtered solution was evaporated to dryness under reduced pressure, and the deliquescent crystalline residue dissolved in water and basified with aqueous sodium carbonate. The crude 5-amino-compound (VI) which separated was collected, dried, and crystallised from petrol (b. p. 40–60°); colourless needles, m. p. 75–76° (Found : C, 71.5; H, 10.4; N, 18.0. $C_{14}H_{22}N_3$ requires C, 71.5; H, 10.6; N, 17.9%).

When dry hydrogen chloride was passed into a solution of the amine in warm petrol, the deliquescent trihydrochloride rapidly crystallised, m. p. 170° (decomp.) (Found : N, 12.25. $C_{14}H_{22}N_3 \cdot 3HCl$ requires N, 12.2%). When the amine was refluxed with acetic acid-acetic anhydride, and the product poured into water and basified with sodium carbonate, the diacetyl derivative slowly crystallised; needles from very dilute aqueous alcohol, m. p. 140–141° (Found : C, 67.2; H, 9.4; N, 13.0. $C_{14}H_{20}O_2N_3$ requires C, 67.6; H, 9.1; N, 13.1%).

α -Diethylamino-*n*-pentan-3-one Diethyl Ketal (cf. van Schelven, B.P. 388,087).—A solution of the amino-ketone (90 g.) in a slight excess of dilute hydrochloric acid was evaporated to dryness under reduced pressure, the residual hydrochloride dissolved in alcohol (100 c.c.) containing dry hydrogen chloride (1 g.), ethyl orthoformate (100 g., 1.2 mols.) added, and the mixture set aside for 8 days. The solution was then partly neutralised by addition of sodium ethoxide (from 12 g. of sodium), filtered from sodium chloride, and shaken with an excess of silver oxide. The filtered solution was fractionally distilled, and the ketal obtained as a colourless liquid, b. p. 116–118°/14 mm. (110 g., 85%).

5-Amino-3-(β -diethylamino- α -methyl-*n*-butylamino)-*o*-xylene (VIII) (6049).—A mixture of the 5-nitro-compound (IV) (10 g.), the diethyl ketal (15.5 g., 1.1 mols.), and ammonium chloride (0.05 g.) was heated in a small distilling flask by means of a metal-bath. As the temperature reached 160° a brisk reaction set in with evolution of ethyl alcohol; when this subsided the temperature was increased to 210° and maintained there for 0.5 hour. The excess of ketal was removed under reduced pressure, and the residual anil dissolved in ethyl alcohol (100 c.c.) and hydrogenated in the presence of Adams's catalyst (0.2 g.) at 60° under a pressure of 90 atm., the almost theoretical absorption of hydrogen (4 mols.) taking 4 hours. The alcohol was then evaporated from the filtered solution, the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour to hydrolyse any traces of unchanged anil, and the solution cooled, basified with sodium carbonate, and extracted with ether, dried, and distilled. A small initial fraction of 3 : 5-diamino-*o*-xylene, b. p. 130°/0.05 mm., was followed by the main fraction, b. p. 170–175°/0.05 mm. This on redistillation gave the amine (VIII) as a pale brown syrup, b. p. 172–174°/0.01 mm. (Found : C, 73.3; H, 11.6; N, 15.3. $C_{14}H_{22}N_3$ requires C, 73.6; H, 11.2; N, 15.2%). The amine slowly darkens on exposure to light. No crystalline salts could be obtained; those prepared were all intractable gums which rapidly darkened when exposed to light.

4-Acetamido-*o*-xylene.—A solution of 4-amino-*o*-xylene (50 g.) in cold acetic acid (50 c.c.) was diluted with water (200 c.c.) and continuously agitated whilst acetic anhydride (50 g., 1.1 mols.) was slowly added. The acetamido-compound readily crystallised and, after the product had been poured into water (2 l.), was collected, washed and dried; m. p. 94–95° (65 g., 97%). Jacobsen (*Ber.*, 1884, 17, 161) acetylated the amine both with acetic acid alone and with acetic acid-acetyl chloride; we find that the use of acetic acid-acetic anhydride gives a syrupy product containing much diacetyl derivative.

3-Nitro-5-acetamido-*o*-xylene (IX).—Crossley and Morrell (*loc. cit.*) give no detailed directions for this preparation. The previous compound (100 g.) was added with stirring to concentrated sulphuric acid (500 c.c.) maintained at –10°, and the resulting solution continuously stirred and kept below –7° whilst a solution of nitric acid (40 c.c., *d* 1.42, 1.05 mols.) in concentrated sulphuric acid (100 c.c.) was

slowly added. The product was poured on crushed ice (ca. 10 kg.), and the solid nitro-compound collected, washed with water, and dried. Recrystallisation from alcohol gave colourless needles, m. p. 207—208° (Found : C, 58.0; H, 6.1. Calc. for $C_{10}H_{12}O_2N_2$: C, 57.7; H, 5.8%).

3-Nitro-5-amino-o-xylene (X).—The acetyl compound was refluxed with 70% sulphuric acid (5 parts) for 30 minutes, and the solution poured on ice and made alkaline with ammonia. The precipitated 5-amino-compound, collected and recrystallised from aqueous alcohol, gave deep orange needles, m. p. 74—75° (Found : C, 57.8; H, 5.9. Calc. for $C_8H_{10}O_2N_2$: C, 57.9; H, 6.0%). This compound has previously been prepared only by the reduction of the 3 : 5-dinitro-derivative (Noelting *et al.*, *loc. cit.*).

4' : 4''-Dichloro-3-nitro-4 : 5-dimethyltriphenylamine (XI).—A mixture of 3-nitro-5-amino-o-xylene (X) (10.5 g.), *p*-chloriodobenzene (16 g., 1.1 mols.), anhydrous potassium carbonate (5 g., 1.2 mols.), copper powder (0.2 g.), potassium iodide (0.05 g.), and dry nitrobenzene (50 c.c.) was gently refluxed with occasional shaking for 7 hours. The product was steam-distilled to remove nitrobenzene and *p*-chloriodobenzene, and the tarry residue dried and extracted (Soxhlet) with petrol (b. p. 40—60°; 250 c.c.). The extract on cooling deposited a reddish-yellow solid, which on crystallisation from alcohol furnished the triphenylamine (XI), pale yellow crystals, m. p. 146—147° (Found : N, 7.3; Cl, 18.1. $C_{30}H_{18}O_2N_2Cl_2$ requires N, 7.2; Cl, 18.3%) (5 g., 20%).

Aqueous dilution of the alcoholic mother-liquor precipitated a red solid, which, crystallised from methyl alcohol, furnished 4'-chloro-3-nitro-4 : 5-dimethyldiphenylamine (see later); m. p. 120—121°. Similar dilution of the methyl-alcoholic mother-liquor gave unchanged (X) (1.5 g.).

4'-Chloro-3-nitro-N-aceto-4 : 5-dimethyldiphenylamide (XII, R = Cl).—A mixture of (IX) (30 g.), *p*-chloriodobenzene (170 g.), anhydrous potassium carbonate (15 g.), copper powder (1 g.), and potassium iodide (0.5 g.) was heated with continuous stirring in a metal-bath at 240° for 4 hours. The cool product was poured into petrol (b. p. 60—80°, 1 l.), and the mixture boiled, filtered, and cooled. The acetodiphenylamide (XII, R = Cl) which separated was once recrystallised from petrol; pale yellow needles, m. p. 121—122° (Found : C, 60.7; H, 4.8; N, 8.9. $C_{18}H_{14}O_2N_2Cl$ requires C, 60.3; H, 4.7; N, 8.8%) (30 g., 70%).

4'-Chloro-3-nitro-4 : 5-dimethyldiphenylamine.—The previous compound was refluxed with 70% sulphuric acid (10 parts) for 30 minutes, and the solution cooled, poured into water, and basified with ammonia. The precipitated diphenylamine was collected and recrystallised from methyl alcohol; orange-red needles, m. p. 121—122° (Found : C, 61.2; H, 4.7; N, 10.3. $C_{14}H_{12}O_2N_2Cl$ requires C, 60.8; H, 4.7; N, 10.1%).

4'-Chloro-3-amino-N-aceto-4 : 5-dimethyldiphenylamide (XIII, R = Cl).—A solution of (XII, R = Cl) (15.5 g.) in alcohol (250 c.c.) was hydrogenated (Adams's catalyst, 0.2 g.) at 50° and 50 atm., theoretical absorption occurring in 3 hours. The filtered solution was evaporated under reduced pressure, and the crystalline residue extracted (Soxhlet) with petrol (b. p. 60—80°, 1 l.). The acetamide (XIII, R = Cl) separated from the extract as colourless crystals, m. p. 118—119° (Found : C, 66.4; H, 6.2. $C_{16}H_{14}ON_2Cl$ requires C, 66.5; H, 5.9%). When hydrogen chloride was passed into an ethereal solution of this amine, the hydrochloride readily crystallised, m. p. 210—212° (decomp.) (Found : C, 58.6; H, 5.7; N, 8.3. $C_{16}H_{14}ON_2Cl \cdot HCl$ requires C, 59.0; H, 5.7; N, 8.6%). The amine also readily afforded a picrate, yellow needles from aqueous alcohol, m. p. 198—199° (decomp.) (Found : C, 51.2; H, 4.2. $C_{16}H_{14}ON_2Cl \cdot C_6H_3O_7N_3$ requires C, 51.0; H, 3.9%).

When the amine was refluxed with dilute hydrochloric acid, the hydrochloride of 4'-chloro-3-amino-4 : 5-dimethyldiphenylamine (6050) separated during the heating in almost theoretical yield; pale pink needles from aqueous alcohol, m. p. 236—237° (decomp.) (Found : C, 59.5; H, 5.8; N, 9.8. $C_{14}H_{12}N_2Cl \cdot HCl$ requires C, 59.3; H, 5.6; N, 9.9%). Addition of aqueous ammonia to a warm aqueous-alcoholic solution of the hydrochloride precipitated the free amine, colourless needles from petrol, m. p. 98—99° (Found : C, 67.6; H, 6.1; N, 11.4. $C_{14}H_{12}N_2Cl$ requires C, 68.1; H, 6.1; N, 11.3%).

When the acetyl derivative (XIII) was hydrolysed with 70% sulphuric acid and the resulting solution poured into water, the sulphate monohydrate separated; colourless needles from alcohol, m. p. 173—174° (Found : C, 55.1; H, 5.6; N, 9.2. $(C_{14}H_{12}N_2Cl)_2 \cdot H_2SO_4 \cdot H_2O$ requires C, 55.1; H, 5.9; N, 8.8%). The yield, however, was now only 40%.

4'-Chloro-3- β -diethylaminoethylamino-4 : 5-dimethyldiphenylamine (XIV, R = Cl) (6051).—A solution of (XIII, R = Cl) (6 g.) in xylene and a solution of β -diethylaminoethyl chloride (1.1 mols.) in xylene (14 c.c., of 30% concentration) were refluxed together for 12 hours, the condensation product separating meanwhile as a heavy oil. The cold mixture was then extracted with 10% aqueous hydrochloric acid (50 c.c.), and the extract refluxed for 1 hour to hydrolyse the acetamido-group. The cold extract was basified with ammonia, the oily deposit extracted with ether, and the dried ethereal extract then distilled. The diphenylamine (XIV, R = Cl) was obtained as a viscous syrup, b. p. 222—223°/0.002 mm. (Found : C, 70.0; H, 8.4; N, 12.4. $C_{30}H_{28}N_3Cl$ requires C, 69.5; H, 8.1; N, 12.15%) (5 g., 70%).

When acetone solutions of this amine and of *p*-toluenesulphonic acid were mixed, the di-*p*-toluenesulphonate crystallised, m. p. 201° (preliminary softening and darkening) (Found : C, 58.9; H, 6.5; N, 6.1. $C_{30}H_{28}N_3Cl_2 \cdot 2C_6H_4SO_3$ requires C, 59.2; H, 6.4; N, 6.1%). This was the only crystalline salt of the base isolated.

4'-Chloro-3-(β -diethylamino- α -methyl-*n*-butylamino)-4 : 5-dimethyldiphenylamine (XVI, R = Cl) (6052).—4'-Chloro-3-amino-4 : 5-dimethyldiphenylamine (11 g.), the diethyl ketal (12 g., 1.1 mols.), and ammonium chloride (0.05 g.) were heated together for 2 hours, initially at 170° and later at 210°. The excess of ketal was removed under reduced pressure, and the residual anil dissolved in alcohol (70 c.c.) and hydrogenated (Adams's catalyst, 0.2 g.) at 60° and 100 atm. for 3 hours. The alcohol was then evaporated from the cold filtered solution, and the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour. The cold solution was basified (sodium hydroxide), extracted with ether, and the dried extract then distilled; the diphenylamine (XVI, R = Cl) was obtained as a pale yellow oil, b. p. 240—242°/0.07 mm. (Found : C, 71.4; H, 8.8; N, 11.0; Cl, 9.2. $C_{25}H_{34}N_3Cl$ requires C, 71.2; H, 8.8; N, 10.8; Cl, 9.2%). No crystalline salts of this amine could be isolated.

3-Nitro-4'-methoxy-4 : 5-dimethyldiphenylamine.—A mixture of (IX) (35 g.), *p*-bromoanisole (180 g.), potassium carbonate (17 g.), copper powder (1 g.), and potassium iodide (0.7 g.) was heated with stirring at 240° for 6 hours in an apparatus so arranged that water formed by slight decomposition could distil away. The cool product was then poured into hot petrol (b. p. 60–80°, 800 c.c.), and the mixture boiled, filtered, evaporated to *ca.* 250 c.c., and then steam-distilled until free from *p*-bromoanisole. The oily residue was then refluxed with 12% hydrochloric acid (120 c.c.) for 1 hour, cooled, and repeatedly extracted with ether until the extracts were colourless. The united, dried extracts on distillation gave the above *diphenylamine* as a viscous red syrup, b. p. 238–240°/0.01 mm. (30 g., 64%); trituration with methyl alcohol induced crystallisation, and the compound then crystallised from *cyclohexane* in orange-yellow plates, m. p. 122–123° (Found: C, 66.5; H, 6.3; N, 10.1. $C_{18}H_{18}O_2N_2$ requires C, 66.2; H, 5.9; N, 10.3%).

3-Amino-4'-methoxy-4 : 5-dimethyldiphenylamine (6053).—A solution of the above compound (30 g.) in alcohol (250 c.c.) was hydrogenated as usual at 50° and 50 atm. for 5 hours. Fractional distillation ultimately gave this *diphenylamine* as a colourless oil, b. p. 220°/0.01 mm., which set to a brittle deliquescent glass, which could not be crystallised (Found: N, 11.3. $C_{18}H_{18}ON_2$ requires N, 11.6%) (22 g., 87%). This compound formed a *picrate* which, recrystallised from very dilute aqueous picric acid, formed fine yellow needles, m. p. 183° (decomp.) (Found: C, 53.25; H, 4.7. $C_{18}H_{18}ON_2 \cdot C_6H_3O_7N_3$ requires C, 53.5; H, 4.5%).

3-β-Diethylaminoethylamino-4'-methoxy-4 : 5-dimethyldiphenylamine (XIV, R = MeO) (6054).—This was prepared precisely similarly to the 4'-chloro-analogue but by using the unacetylated diphenylamine, and obtained initially as a crude fraction, b. p. 235–240°/0.06 mm., which on refractionation gave the pure *diphenylamine* as a colourless oil, b. p. 238°/0.01 mm. (Found: N, 12.6. $C_{21}H_{21}ON_2$ requires N, 12.3%) (60%).

3-δ-Diethylamino-α-methyl-n-butylamino-4'-methoxy-4 : 5-dimethyldiphenylamine (XVI, R = MeO) (6055).—This compound was also prepared precisely similarly to the 4'-chloro-analogue and obtained as a pale green oil, b. p. 210°/0.002 mm. (Found: C, 74.8; H, 9.3; N, 11.3. $C_{26}H_{28}ON_2$ requires C, 75.2; H, 9.7; N, 11.0%): 58% of the theoretical.

No crystalline salts of the last two amines could be isolated.

This research was carried out on behalf of the Medical Research Council under a wartime collaborative agreement on antimalarial research between the Medical Research Council and Imperial Chemical Industries Ltd. We are greatly indebted to the Council for a grant (J. W. G. P.) and to Imperial Chemical Industries Ltd. both for materials and for carrying out the antimalarial tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

[Received, September 30th, 1946.]

169. Synthetic Antimalarials. Part XIX. Dialkylaminoalkylaminodiphenylguanidines.

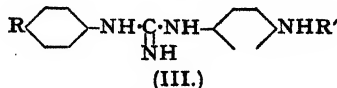
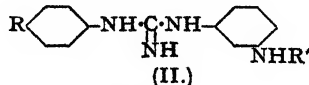
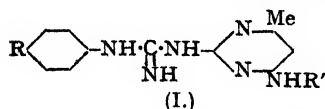
By FREDERICK G. MANN, FREDERICK T. NAYLOR, and J. W. GEOFFREY PORTER.

The study of the effect on antimalarial activity caused by replacing the pyrimidine by the benzene ring has been extended to include the diphenylguanidines of types (II) and (III), the former being the benzene analogues of the active 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines of type (I).

The scope of the investigation was restricted by the intractable nature of many of the products.

IN Part XVIII (Mann and Porter, preceding paper) an attempt was made to ascertain whether the marked antimalarial properties of the 2-*p*-chloroanilino-4-dialkylaminoalkylamino-6-methylpyrimidines were determined primarily by their general molecular structure, or more specifically by the presence and properties of the constituent pyrimidine ring. This factor was investigated by preparing analogous compounds differing only in that the pyrimidine ring of the former compounds had now been replaced by a benzene ring. The compounds so prepared, of the general type 4'-chloro-3-dialkylaminoalkylamino-4 : 5-dimethyldiphenylamine, were found to be without antimalarial activity.

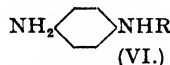
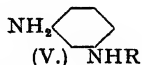
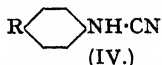
It was clearly desirable, however, that the evidence concerning this factor should not be limited to one class of pyrimidine derivative. The 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines (Curd and Rose, *J.*, 1946, 362) (I) constitute a second class of pyrimidine derivative having high antimalarial activity, and it was considered of interest,



therefore, to prepare their benzene analogues, *i.e.*, diphenylguanidines of type (II). Furthermore, in order to determine whether the position of the dialkylaminoalkylamino-

substituent relative to that of the guanidine nucleus has any marked influence on the antimalarial activity, the preparation of the *pp'*-disubstituted diphenylguanidines of type (III) was investigated.

The most convenient method for the preparation of asymmetrically disubstituted diaryl guanidines is the interaction of an aryl cyanamide with the hydrochloride of an arylamine (Heller and Bauer, *J. pr. Chem.*, 1902, **65**, 384). Thus *p*-chlorophenylcyanamide (IV, R = Cl) condensed with *N*- β -diethylaminoethyl-*m*-phenylenediamine (V, R = CH₂·CH₂·NEt₂) in alcoholic hydrogen chloride to afford *N*-*p*-chlorophenyl-*N'*-*m*- β -diethylaminoethylaminophenylguanidine (II, R = Cl, R' = CH₂·CH₂·NEt₂) in moderate yield. A similar condensation between (IV, R = Cl) and *N*- β -diethylaminoethyl-*p*-phenylenediamine furnished *N*-*p*-chlorophenyl-*N'*-*p*- β -diethylaminoethylaminophenylguanidine (III, R = Cl, R' = CH₂·CH₂·NEt₂). Both the above guanidines were crystalline compounds.



N- β -Diethylaminoethyl-*m*-phenylenediamine has previously been prepared (U.S.P. 1,757,394) by heating *m*-phenylenediamine with β -diethylaminoethyl chloride. A more convenient preparation both of this compound and of *N*- β -diethylaminoethyl-*p*-phenylenediamine consists in the condensation of β -diethylaminoethyl chloride and the corresponding nitroaniline to give the hydrochloride of 1-nitro-3- β -diethylaminoethylamino- and of 1-nitro-4- β -diethylaminoethylamino-benzene. Catalytic reduction of these hydrochlorides afforded good yields of the phenylenediamines (V and VI, R = CH₂·CH₂·NEt₂).

With the object of preparing the analogous guanidines carrying the δ -diethylamino- α -methyl-*n*-butyl side chain, *N*- δ -diethylamino- α -methyl-*n*-butyl-*m*- and -*p*-phenylenediamine (V and VI, R = CHMe·[CH₂]₃·NEt₂) were prepared by condensing the appropriate nitroaniline with δ -diethylamino-*n*-pentan-2-one diethyl ketal and reducing the resulting anil to give the required product (cf. Mann and Porter, *loc. cit.*). Although both these substituted phenylenediamines appeared to react with (IV, R = Cl) under the usual conditions, the products proved to be intractable, deliquescent gums which could neither be crystallised nor induced to give crystalline salts. Dewar (*J.*, 1944, 534) has noted similar difficulties in attempting to crystallise *N*-dialkylaminoalkyldiarylguanidines.

Attempts were next made to prepare compounds of types (II) and (III) in which R = OMe. *p*-Methoxyphenylthiourea (Dienske, *Rec. Trav. chim.*, 1931, **50**, 407) was treated with lead hydroxide to give *p*-methoxyphenylcyanamide (IV, R = OMe). This reacted normally with each of the above four substituted phenylenediamines but no crystalline product could be isolated. Analysis of the resinous gum produced by the reaction between (IV, R = OMe) and *N*- β -diethylaminoethyl-*p*-phenylenediamine showed it to be almost certainly the required *N*-*p*-methoxyphenyl-*N'*-*p*- β -diethylaminoethylaminophenylguanidine (III, R = OMe, R' = CH₂·CH₂·NEt₂).

An alternative synthetic route was equally unproductive of crystalline products. *p*-Methoxyphenylcyanamide was heated in alcoholic solution with *m*-nitroaniline hydrochloride to form *N*-*p*-methoxyphenyl-*N'*-*m*-nitrophenylguanidine hydrochloride which was catalytically reduced to *N*-*p*-methoxyphenyl-*N'*-*m*-aminophenylguanidine hydrochloride (II, R = OMe, R' = H). The latter compound, however, did not condense normally with β -diethylaminoethyl chloride: a complex mixture of products, arising apparently from the rupture of the guanidino-linkage, being isolated.

Only the two crystalline guanidine derivatives (II and III, R = Cl, R' = CH₂·CH₂·NEt₂) have been tested. Whereas the former (5220) showed significant activity (+ to ++ at 80 mg./kg.) the latter (6180) was inactive at the same dosage (highest tested). The former is the more closely related to the active 2-arylguanidino-4-dialkylaminoalkylaminopyrimidines of type (I), and the conclusion may therefore perhaps be drawn that the replacement of a pyrimidine ring by a benzene ring in an antimalarial structure based on pyrimidine does not necessarily lead to complete loss of activity despite the results given in the previous paper. In this connection it may be noted that, whereas the diphenylamines described in the previous paper do not retain any of the tautomeric possibilities characteristic of their pyrimidine analogues, the diphenylguanidine (II, R = Cl, R' = CH₂·CH₂·NEt₂) is not devoid of all the tautomeric possibilities existent in type (I).

EXPERIMENTAL.

1-Nitro-3- β -diethylaminoethylaminobenzene.—A mixture of *m*-nitroaniline (100 g.) and β -diethylaminoethyl chloride (105 g., 1.1 mols.) in xylene (500 c.c.) was refluxed for 3 hours. The crystalline

hydrochloride was then collected and recrystallised from ethyl alcohol–light petroleum (b. p. 60–80°) (equal vols.); pale yellow needles, m. p. 177–178° (Found: N, 15.3; Cl, 13.2. $C_{12}H_{19}O_2N_2 \cdot HCl$ requires N, 15.4; Cl, 13.0%). Yield, 140 g.; 70%.

Basification of an aqueous solution of the hydrochloride furnished the oily base (Found: C, 60.35; H, 8.1; N, 17.7. $C_{12}H_{19}O_2N_2$ requires C, 60.7; H, 8.1; N, 17.7%). The base readily afforded a *picrate*, orange crystals from alcohol, m. p. 149–150° (Found: N, 18.2. $C_{12}H_{19}O_2N_2 \cdot C_6H_3O_7N_3$ requires N, 18.0%).

1-Nitro-4- β -diethylaminoethylaminobenzene hydrochloride was similarly prepared and recrystallised; yellow needles, m. p. 159–160° (Found: C, 52.35; H, 7.6; N, 15.3. $C_{12}H_{19}O_2N_2 \cdot Cl$ requires C, 52.6; H, 7.6; N, 15.4%). Yield, 72%. The *picrate*, yellow needles from ethyl alcohol, had m. p. 168–169° (Found: N, 18.5. $C_{12}H_{19}O_2N_2 \cdot C_6H_3O_7N_3$ requires N, 18.0%).

N- β -Diethylaminoethyl-*m*-phenylenediamine (V, $R = CH_2 \cdot CH_2 \cdot NEt_2$).—A solution of 1-nitro-3- β -diethylaminoethylaminobenzene hydrochloride (140 g.) in 90% aqueous ethyl alcohol (350 c.c.) was hydrogenated (Adams's catalyst, 0.3 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated and then basified with aqueous sodium hydroxide. The product was extracted with ether and the dried extract fractionally distilled. The pure *amine* had b. p. 154°/0.05 mm. (Found: C, 69.2; H, 10.4; N, 19.9. $C_{12}H_{19}N_3$ requires C, 69.5; H, 10.3; N, 20.3%). Yield, 106 g.; 85%.

N- β -Diethylaminoethyl-*p*-phenylenediamine (VI, $R = CH_2 \cdot CH_2 \cdot NEt_2$) was similarly prepared as a hygroscopic oil, b. p. 156°/0.02 mm. (Found: C, 69.1; H, 10.8; N, 21.0%).

p-Chlorophenylcyanamide (IV, $R = Cl$).—This compound was prepared from *p*-chlorophenylthiourea and obtained as colourless needles, m. p. 103° (Found: N, 18.4. Calc. for $C_7H_5N_2Cl$: N, 18.3%).

N-*p*-Chlorophenyl-*N'*-*m*- β -diethylaminoethylaminophenylguanidine (II, $R = Cl$, $R' = CH_2 \cdot CH_2 \cdot NEt_2$).—A solution of (IV, $R = Cl$) (10 g.) and *N*- β -diethylamino-*m*-phenylenediamine (13 g., 1 mol.) in ethyl alcohol (50 c.c.) containing hydrogen chloride (2.5 g., 2 mols.) was refluxed for 20 hours. The whole was then poured into 5% acetic acid (300 c.c.) and filtered, and the filtrate was slowly run into an excess of ice-cold 10% aqueous sodium hydroxide. The sticky white solid which separated was collected and dried. Prolonged extraction (Soxhlet) with light petroleum (b. p. 60–80°) afforded the crude product, which readily separated from the hot solution. Recrystallisation from light petroleum gave the pure *guanidine*, m. p. 112–113° (Found: C, 63.8; H, 6.9; N, 19.5. $C_{19}H_{28}N_6$ requires C, 63.4; H, 7.3; N, 19.5%). Yield, 3.8 g.; 17%.

N-*p*-Chlorophenyl-*N'*-*p*- β -diethylaminoethylaminophenylguanidine (III, $R = Cl$, $R' = CH_2 \cdot CH_2 \cdot NEt_2$).—A solution of (IV, $R = Cl$) (11.8 g.) and *N*- β -diethylamino-*p*-phenylenediamine (16.4 g., 1 mol.) in ethyl alcohol (55 c.c.) containing hydrogen chloride (2.85 g., 2 mols.) was refluxed for 24 hours. The solution was then evaporated and the residue was triturated with a slight excess of 5% aqueous ammonia. The resulting gum was washed by stirring with water and dried. Repeated extraction with light petroleum (b. p. 40–60°) afforded the *guanidine* which was once recrystallised from light petroleum; colourless plates, m. p. 102–103° (Found: C, 63.5; H, 7.5; N, 19.0%). Yield, 5 g.; 18%.

N- δ -Diethylamino- α -methyl-*n*-butyl-*m*-phenylenediamine (V, $R = CHMe \cdot [CH_2]_3 \cdot NEt_2$).—*m*-Nitroaniline (50 g.), δ -diethylamino-*n*-pentan-2-one diethyl ketal (88 g.), and ammonium chloride (0.05 g.) were heated together for 2 hours, initially at 170° and later at 210°. The excess of ketal was removed under reduced pressure and the residual anil was dissolved in alcohol (200 c.c.) and hydrogenated (Adams's catalyst, 0.2 g.) at 60° and 100 atmospheres during 3 hours. The filtered solution was evaporated and the residue refluxed with 15% hydrochloric acid (400 c.c.) for $\frac{1}{2}$ hour. The cold solution was basified (sodium hydroxide) and extracted with ether, and the dried extract was distilled. The *amine* was obtained as a colourless oil, b. p. 168°/0.01 mm. (Found: C, 72.1; H, 11.1; N, 17.0. $C_{18}H_{27}N_3$ requires C, 72.3; H, 10.8; N, 16.9%). Yield, 50 g.; 55%.

N- δ -Diethylamino- α -methyl-*n*-butyl-*p*-phenylenediamine (VI, $R = CHMe \cdot [CH_2]_3 \cdot NEt_2$) was similarly prepared, except that the temperature during anil formation was not raised above 180°, since a higher temperature caused spontaneous decomposition. This *amine*, a colourless oil, had b. p. 174°/0.05 mm. (Found: C, 71.9; H, 10.7; N, 16.9%). Yield, 20 g.; 23%.

p-Methoxyphenylcyanamide (IV, $R = OMe$).—*p*-Methoxyphenylthiourea (30 g.), potassium hydroxide (43 g.), lead acetate (85 g.), and water (430 c.c.) were stirred during heating on a steam-bath for 15 minutes. The lead sulphide was then collected, and the filtrate acidified with 10% acetic acid and cooled. The crude product was filtered off, dissolved in 5% sodium hydroxide (150 c.c.), and cautiously reprecipitated by the addition of 5% acetic acid. Careful neutralisation resulted in the almost complete separation of a pale yellow amorphous material (ca. 1 g.) which was collected; acidification of the filtrate then caused the required product to separate in short needles. A second similar purification gave the *cyanamide* as colourless needles, m. p. 86–87° (Found: C, 64.8; H, 5.6. $C_8H_9ON_2$ requires C, 64.8; H, 5.4%). 10 g., 40%.

N-*p*-Methoxyphenyl-*N'*-*m*-nitrophenylguanidine.—*p*-Methoxyphenylcyanamide (7 g.) and *m*-nitroaniline hydrochloride (8.5 g., 1 mol.) were dissolved in alcohol (35 c.c.) and heated under reflux for 24 hours. The whole was then poured into 2% acetic acid (1 l.) and filtered. The filtrate was basified (sodium hydroxide) and the crude product collected. Two recrystallisations from 50% aqueous alcohol gave the pure *guanidine*, orange-red needles, m. p. 142° (Found: C, 58.3; H, 5.2; N, 19.6. $C_{14}H_{14}O_3N_4$ requires C, 58.7; H, 4.9; N, 19.6%). 8 g., 55%. The hydrochloride formed colourless needles, m. p. 128–136° (Found: C, 52.5; H, 4.6; N, 17.2. $C_{14}H_{14}O_3N_4 \cdot HCl$ requires C, 52.1; H, 4.7; N, 17.4%).

N-*p*-Methoxyphenyl-*N'*-*m*-aminophenylguanidine Hydrochloride (II, $R = OMe$, $R' = H$).—A solution of the above hydrochloride (8 g.) in alcohol (200 c.c.) was hydrogenated (Adams's catalyst, 0.2 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated to ca. 50 c.c. and, on cooling, the *amino-guanidine* hydrochloride crystallised. Recrystallisation from alcohol gave small crystals, m. p. 212° (Found: C, 57.8; H, 6.0; N, 20.1. $C_{14}H_{14}ON_4 \cdot HCl$ requires C, 57.4; H, 5.9; N, 20.05%). Yield, 5 g.; 70%.

N-*p*-Methoxyphenyl-*N'*-*p*- β -diethylaminoethylaminophenylguanidine (III, $R = OMe$, $R' = CH_2 \cdot CH_2 \cdot NEt_2$).—*p*-Methoxyphenylcyanamide (7.5 g.) and *N*- β -diethylaminoethyl-*p*-phenylenediamine

(10.5 g.) were dissolved together in ethyl alcohol (35 c.c.) containing hydrogen chloride (2.9 g.) and refluxed for 36 hours. Evaporation followed by trituration of the residue with 5% aqueous ammonia gave a brown gum which was washed and dried. Repeated extraction with hot light petroleum (b. p. 40–60°) afforded, on cooling, a pale brown gum (1 g.). This was shaken with ether (20 c.c.), the ethereal solution evaporated, and the residue re-extracted with hot light petroleum. On cooling, the *guanidine* separated as a pale brown gum which was almost pure (Found: C, 68.3; H, 8.7; N, 19.1. $C_{20}H_{22}ON_5$ requires C, 67.6; H, 8.2; N, 19.7%). Yield, 0.7 g.; 4%. Neither the base nor any salts could be obtained crystalline.

This research was carried out on behalf of the Medical Research Council under a wartime collaborative agreement on antimalarial research between the Medical Research Council and Imperial Chemical Industries Ltd. We are greatly indebted to the Council for grants (F. T. N., J. W. G. P.) and to Imperial Chemical Industries Ltd., both for materials and for carrying out the antimalarial tests.

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[Received, September 30th, 1946.]

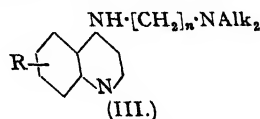
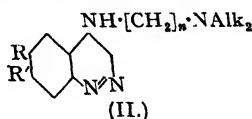
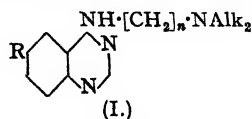
170. Synthetic Antimalarials. Part XX. Cinnolines. Part XIII. Synthesis and Antimalarial Action of 4-Aminoalkylaminocinnolines.

By J. R. KENEFORD and J. C. E. SIMPSON.

The preparation of a series of 6- and 7-substituted 4-aminoalkylaminocinnolines is described, and their antimalarial activities are recorded.

THE cinnoline ring-system is one which has obvious potentialities as a vehicle for the production of chemotherapeutic agents. As a result of earlier work (*J.*, 1942, 353; 1943, 447; 1945, 512, 520; 1946, 673; this vol., pp. 227, 232) having as its objective the consolidation of routes leading to different types of 4-substituted cinnolines, we were in a position to investigate the chemotherapeutic possibilities which this field appeared to offer, and we decided first to attempt to prepare compounds having antimalarial activity. Our interest in this problem was given additional stimulus by the fact that, when the work was begun, the bulk of the published synthetic work relating to the chemotherapy of malaria was restricted to derivatives of acridine and quinoline, although a few aminoalkylaminoquinazolines of type (I; R = Cl or NO₂) had been synthesised by Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, 8, 1797; *Chem. Abs.*, 1939, 33, 4993); these compounds, however, were stated to be devoid of antimalarial activity.

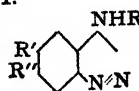
Preliminary results with cinnoline derivatives of type (II; R = H or OMe; R' = H) (Simpson and Schofield, *Nature*, 1946, 157, 439) suggested that activity might be expected in suitably substituted compounds, and in this paper we describe the preparation of a series of derivatives of type (II) substituted at C₆ and C₇. In choosing these positions of nuclear substitution we were guided partly by the accessibility of intermediates and partly by the fact that antimalarial activity is recorded for 4-aminoalkylaminoquinolines substituted in the same positions (III; R at C₆ or C₇) (Schönhöfer, *Z. physiol. Chem.*, 1942, 274, 1; B.P. Appl. 27673/38).



The compounds listed in Table III were prepared by conversion of the requisite 4-hydroxycinnoline (*J.*, 1945, 520; this vol., pp. 227, 232) into the 4-chloro- and thence into the 4-phenoxy-derivative, followed by condensation of the latter with the appropriate amine; the use of phenoxy- instead of chloro-compounds for this reaction was more convenient, as most 4-chlorocinnolines decompose on storage, whereas the phenoxy-compounds can be kept indefinitely. The yield of 7-chloro-4-hydroxycinnoline was raised from 30% (this vol., p. 232) to 90% by the use of concentrated hydrochloric acid for the final stage, and we have found that this modification is of general applicability to the preparation in high yield of 4-hydroxycinnolines which do not contain an electron-attractive group in positions 6 or 8.

The compounds (I) were tested against *P. gallinaceum* in chicks at the Blackley laboratories of Imperial Chemical Industries Limited by the method of Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, 39, 139), and the results [including, for purposes of comparison, those of Simpson and Schofield (*loc. cit.*)] are shown in Table I. Inspection of these results leads to the following conclusions: (a) Combination of the side-chain characteristic of mepacrine and

TABLE I.

Compounds of type 

Ref. No.	R.	R'.	R''.	Dose (mg./kg.).	Activity.*
3309	CHMe·[CH ₂] ₃ ·NEt ₃	H	H	250 120	++ +
6022	"	H	Cl	80 40	++ ++
5655	"	Cl	H	160 80	+ to ++ —
5654	"	Br	H	160 80	+ to ++ —
4404	"	OMe	H	80	—
5656	"	Cl	Cl	160 80 40	++ + to ++ —
5659	"	Cl	Me	20 160 80	— + to ++ +
3602	[CH ₂] ₃ ·NEt ₂	H	H	200 120	± —
6024	"	H	Cl	80	+
5853	"	Cl	Cl	80	—
6023	[CH ₂] ₃ ·NEt ₂	H	Cl	80 40	++ +
5852	"	Cl	Cl	80	+
6021	[CH ₂] ₃ ·NMe ₂	H	Cl	80 40	+ to ++ +
5657	"	Cl	Cl	160 80	+ to ++ ±
5658	"	Cl	Me	160 80	+ to ++ +
6025	[CH ₂] ₃ ·NBu ₂	H	Cl	80	+
5854	"	Cl	Cl	80	—
6026	[CH ₂] ₃ ·N·C ₈ N ₁₀	H	Cl	80	+
5855	"	Cl	Cl	80	—

* Activity is shown as marked (++), slight (+), doubtful (±), or inactive (—).

pamaquin with a suitably substituted nucleus results in considerably greater activity than does the combination of other side-chains with the same nuclei (compare, *e.g.*, 3309, 6022, 5656 with 3602, 6024, 5853); (b) substitution at C₇, *ceteris paribus*, increases the antimalarial activity; (c) substitution at C₈ exerts a pronounced dystherapeutic effect. These conclusions are meant to apply only to the range of compounds studied; a discussion of their possible significance is held over pending the accumulation of further data.

The following compounds were tested for prophylactic activity against *P. gallinaceum* in chicks by the method of Davey (*Ann. Trop. Med. Parasit.*, 1946, 40, 52) but found to be inactive; 5654, 5659, 6022, 6023, and 6024 at 80 mg./kg., and 6024, 6025, and 6026 at 160 mg./kg.

A paper by Leonard and Boyd (*J. Org. Chem.*, 1946, 11, 419), which appeared after completion of this work, describes the preparation of 6023 and of 6-bromo-4-γ-diethylaminopropyl-

TABLE II.

4-Phenoxyinnolines.

					Analysis.					
Substituent at		M. p.	Formula.	Crystalline form.	Found, %.			Required, %.		
6.	7.				C.	H.	N.	C.	H.	N.
H	H	94—95°	C ₁₄ H ₁₀ ON ₂	Colourless needles or leaflets ¹	75.5	4.45	12.9	75.6	4.55	12.6
H	Cl	127—128	C ₁₄ H ₉ ON ₂ Cl	Colourless needles ²	65.4	3.7	—	65.5	3.55	—
Cl	H	128—129	C ₁₄ H ₉ ON ₂ Cl	" ²	65.2	3.45	—	65.5	3.55	—
Br	H	151.5—152	C ₁₄ H ₉ ON ₂ Br	" ²	55.6	3.2	—	55.8	3.0	—
OMe	H	108—109	C ₁₅ H ₁₁ ON ₂	" ³	71.0	4.45	—	71.4	4.8	—
Cl	Me	154—155	C ₁₅ H ₁₁ ON ₂ Cl	" ²	66.2	3.95	10.6	66.5	4.1	10.35

¹ From ether-ligroin (b. p. 40—60°).

² From aqueous alcohol.

³ From alcohol.

TABLE III.
4-Aminoalkylaminocinnolines.

Ref. No.	Substituent at 4.		M. p.	Formula.	Reaction conditions.	Crystalline form.	Analysis.					
							Found, %.			Required, %.		
	4.	6.	7.				C.	H.	N.	C.	H.	N.
5655	NH·CHMe·[CH ₂] ₃ ·NEt ₃	Cl	H	107—108°	C ₁₇ H ₂₃ N ₄ Cl	150°/2 hr.	63.3	8.05	—	11.25	63.6	7.85
5654	"	Br	H	97.5—98.5	C ₁₇ H ₂₃ N ₄ Br	150°/2 hr.	55.6	7.05	15.35	—	55.9	6.9
5656	"	Cl	Cl	121.5—123	C ₁₇ H ₂₃ N ₄ Cl ₂	130°/2½ hr.	57.45	6.55	15.2	20.2	57.4	6.8
5659	"	Cl	Me	120—121	C ₁₈ H ₂₇ N ₄ Cl	170°/2½ hr.	64.75	8.25	16.7	—	64.55	8.1
6022	"	H	Cl	123.5—124.5	C ₁₇ H ₂₃ N ₄ Cl	150°/2 hr.	63.65	7.8	17.2	—	63.6	7.9
5853	NH·[CH ₂] ₃ ·NEt ₃	Cl	Cl	204—204.5	C ₁₄ H ₁₉ N ₄ Cl ₂	130°/¼ hr.	53.9	5.7	17.75	—	53.7	5.8
6024	"	H	Cl	182.5—183.5	C ₁₄ H ₁₉ N ₄ Cl	"	60.4	6.65	19.7	—	60.3	6.9
5657	NH·[CH ₂] ₃ ·NMe ₂	Cl	Cl	170—171	C ₁₃ H ₁₈ N ₄ Cl ₂	"	52.45	5.4	18.75	23.85	52.2	5.4
5658	"	Cl	Me	168—170	C ₁₄ H ₁₉ N ₄ Cl	"	60.35	6.85	19.85	—	60.3	6.9
6021	"	H	Cl	175—176	C ₁₃ H ₁₇ N ₄ Cl	"	59.1	6.65	20.75	—	58.95	6.5
5852	NH·[CH ₂] ₃ ·NEt ₃	Cl	Cl	151.5—152.5	C ₁₅ H ₂₀ N ₄ Cl ₂	"	55.35	6.15	17.1	—	55.0	6.2
6023	"	H	Cl	162—163	C ₁₅ H ₂₁ N ₄ Cl	"	61.45	7.4	18.9	—	61.5	7.2
5854	NH·[CH ₂] ₃ ·NBu ₂	Cl	Cl	153.5—154	C ₁₈ H ₂₈ N ₄ Cl ₂	"	59.5	7.25	—	18.35	59.5	7.4
6025	"	H	Cl	123—124	C ₁₉ H ₂₉ N ₄ Cl	"	65.3	8.3	15.7	—	65.4	8.4
5855	NH·[CH ₂] ₃ ·N·C ₃ H ₁₀	Cl	Cl	214—215	C ₁₈ H ₂₆ N ₄ Cl ₂	"	56.95	6.05	—	21.3	56.6	5.95
6026	"	H	Cl	180—181	C ₁₈ H ₂₆ N ₄ Cl	"	62.55	7.1	18.15	—	63.0	6.95

¹ From ether.² From ethyl acetate.³ Leonard and Boyd (*loc. cit.*) give m. p. 164—165°.³ From alcohol.⁴ From benzene-ligroin (b. p. 80—80°).⁴ From benzene.

aminocinnoline; these compounds, for which no antimalarial results are yet recorded, were made directly from the chlorocinnolines and the amine.

EXPERIMENTAL.

M. ps. are uncorrected Derivatives of 4-hydroxy- and 4-hydroxy-6-methoxy-cinnoline were prepared by Dr. K. Schofield. All the reactions could apparently be carried out on any desired scale without loss of yield.

Improved Preparation of 7-Chloro-4-hydroxycinnoline.—Diazotisation was effected in hydrochloric acid, followed by heating on the steam-bath at 60° (cf. this vol., p. 232). It was found that the yield of cinnoline increased with an increase in concentration of acid up to ca. 8.5N; the yield was then 90–95%, and no significant increase resulted with higher concentrations. The ratio amino-ketone : acid medium varied between 1 : 60 and 1 : 100.

Similar results were obtained in the preparation of 4-hydroxycinnoline (70–75% yield in 9–9.5N-hydrochloric acid; contrast *J.*, 1945 520); amino-ketone : acid medium = ca. 1 : 100.

In each set of experiments the acid concentrations were calculated after addition of the nitrite solution, and the time of reaction was 4–5 hours. The products were isolated by evaporation under reduced pressure (this gave 4-hydroxycinnoline as hydrochloride, but in the case of the 7-chloro-compound much free base crystallised from the reaction mixture).

Preparation of 4-Chlorocinnolines.—The appropriate 4-hydroxycinnoline (1 mol.), phosphorus pentachloride (ca. 2 mols.), and phosphorus oxychloride (ca. 6 mols.) were heated on the steam-bath for 1 hour. The reaction was usually rapid; the hydroxycinnoline dissolved, and the chlorocinnoline crystallised from the hot solution. The mixture was poured on ice, made just alkaline with aqueous sodium hydroxide, and extracted with ether. The extract was washed with very dilute sodium hydroxide and water, dried, and concentrated (in the case of 4-hydroxycinnoline this was done under reduced pressure); yields of crude products were 80–90%. 4-Anilino-cinnolines, by which the chlorocinnolines were occasionally characterised, were made by warming the reactants on the steam-bath for a few minutes, followed by crystallisation of the products from alcohol or ammoniacal alcohol.

4-Chlorocinnoline formed very pale yellow needles, m. p. 78–79°, from ether-ligroin (b. p. 40–60°); Busch and Klett (*Ber.*, 1892, 25, 2847) and Leonard and Boyd (*loc. cit.*) give m. p. 79° and 76–77° respectively. The compound is unstable and decomposes very rapidly when warmed either alone or with acids. 4-Anilino-cinnoline formed pale yellow silky needles, m. p. 229.5–230.5° (Busch and Klett, *loc. cit.*, give m. p. 232°) (Found : N, 19.0. Calc. for $C_{14}H_{11}N_3$: N, 19.0%). 4-Chloro-6-bromocinnoline, pale yellow needles, had m. p. 136–138° [Leonard and Boyd, *loc. cit.*, give 136–137° and 127–128° (interconvertible)]. 4 : 7-Dichlorocinnoline formed colourless polyhedra, m. p. 143–144° (Found : C, 48.3; H, 2.1; Cl, 35.4. Calc. for $C_8H_4N_2Cl_2$: C, 48.2; H, 2.0; Cl, 35.7%). Leonard and Boyd give m. p. 143–143.5°. The 4 : 6-isomer, soft pale yellow needles, had m. p. 111–112°, and 4 : 6-dichloro-7-methylcinnoline crystallised in small cream-coloured needles, m. p. 176–177°. 4-Chloro-6-methoxycinnoline formed colourless hair-like needles, m. p. 149–151°, from ether (Found : Cl, 18.4. $C_9H_7ON_2Cl$ requires Cl, 18.25%), and yielded 4-anilino-6-methoxycinnoline (pale yellow needles, m. p. 235.5–236°) (Found : C, 71.6; H, 5.25. $C_{14}H_{13}ON_3$ requires C, 71.7; H, 5.2%).

Preparation of 4-Phenoxycinnolines.—The chloro-compound (1 mol.) was added to a solution of powdered potassium hydroxide (1.2 mols.) in phenol (ca. 7.5 mols.), and the whole was heated on the steam-bath for 1 hour (the reaction with 4-chloro-6-methoxycinnoline was sluggish, and a reaction time of 6 hours was used). The mixture was poured into excess of aqueous sodium hydroxide and extracted with ether, after which the extract was repeatedly washed with sodium hydroxide solution and water, dried, and concentrated, giving the phenoxy-compounds (see Table II) in yields of 80–95%.

Preparation of 4-Aminoalkylaminocinnolines.—The phenoxy-compound (1 mol.) and aliphatic amine (ca. 2 mols.) were heated in an oil-bath, completion of the reaction being ascertained by examination of a sample of the material which (except in the reactions with δ -diethylamino- α -methylbutylamine) crystallised on cooling. The cold mixtures were filtered after addition of ether and the solid bases crystallised from the appropriate solvent (yields, 90–95%). The reactions in which δ -diethylamino- α -methylbutylamine was used were more sluggish than those with other amines, and the products from them were worked up by basification with aqueous sodium hydroxide and extraction with ether; the ethereal solutions were extracted with 33% aqueous acetic acid, the latter basified, and the products again taken into ether, which was washed, dried, and evaporated; excess of fatty amine was then removed at 90–110°/0.2–0.5 mm., and the residues recrystallised (yields were 65–75%). Distillation of the aminoalkylaminocinnolines was unsuccessful in the few cases tried owing to decomposition. 4404 was prepared by heating the chloro-compound and amine in phenol at 170°; 3602 was formed when 4-chlorocinnoline and the amine were heated at 130° without solvent under nitrogen, but was best prepared *via* the phenoxy-compound.

This investigation was carried out as part of a wartime programme of antimalarial research sponsored by the Medical Research Council in collaboration with Imperial Chemical Industries Limited. We are indebted to the former for a Research Studentship (J. R. K.) and to the latter for materials and for carrying out the biological tests. We are also greatly indebted to the workers of Imperial Chemical Industries for many discussions on the above work.

171. *The Effect of Temperature on the Proportions of Isomers formed in the Mononitration of Toluene.*

By W. W. JONES and M. RUSSELL.

Toluene has been nitrated with mixtures of nitric and sulphuric acids at various temperatures from -30° to 60° . The proportion of *m*-nitrotoluene formed in each instance has been calculated from the setting point of the derived TNT. The results afford evidence that in applying the Arrhenius equation $k = nAe^{-E/RT}$ to the mononitration of toluene, $A_p = 2.90 A_m$, $A_p = 2.70 A_m$, $E_m - E_o = 917$ and $E_m - E_p = 1103$ cal. deg. $^{-1}$ mol. $^{-1}$.

THE manufacture of trinitrotoluene is complicated by the undesirable formation of *m*-nitrotoluene in the mononitration stage. Several workers have published data on the proportions of isomers formed in the mononitration of toluene at various temperatures and in several media. Their results, for percentage *m*-nitrotoluene, are collected in Table I. Generally

TABLE I.

Temp.	A.	B.	C.			D.	E.
			a.	b.	c.		
-30°	2.7	3.5	—	—	—	—	—
0	3.1	3.9	2.5	4.5	3.3	3.7	—
20	—	—	4.3	4.5	3.9	—	4.1
30	3.2	4.4	—	—	—	4.4	—
40	—	—	—	4.2	—	—	—
50	—	—	—	4.3	—	—	—
60	4.0	5.1	—	—	—	—	—

A. Van den Arend, *Rec. Trav. chim.*, 1909, **28**, 408. Nitration in 85% HNO_3 .B. Holleman, Vermeulen, and de Mooy, *ibid.*, 1914, **33**, 1. Recalculation of results of Van den Arend.C. Gibson, Duckham, and Fairbairn, *J.*, 1922, **121**, 270. Nitration in:(a) 94% HNO_3 ;(b) Mixed acid containing 58.7% H_2SO_4 , 23.8% HNO_3 , 17.5% H_2O ;(c) Mixed acid containing 64.4% H_2SO_4 , 13.7% HNO_3 , 21.9% H_2O .D. Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959. Nitration in acetic anhydride and in nitromethane.E. de Beule, *Bull. Soc. chim. Belg.*, 1933, **42**, 27. Nitration in HNO_3 and mixed acid.

the proportions of isomers were determined by thermal analysis, but Ingold *et al.* (*loc. cit.*) also determined the meta-content by solubility measurements on the derived nitrobenzoic acids.

The figures recorded in Table I show rather wide variations and, in particular, they indicate that change in meta-nitration with temperature is much less for nitration in mixed acid than in other media. Because of its technical importance, nitration in mixed acid has been reinvestigated, using a new method of analysis which is simpler and considered to be less liable to error than thermal analysis.

2:4-Dinitrotoluene, *p*-nitrotoluene, and known mixtures of *m*- and *p*-nitrotoluene were trinitrated by the standard method described in the experimental part, and the setting points of

TABLE II.

Concn. of <i>m</i> -nitrotoluene (%)	2:4-DNT.	Mixtures of <i>m</i> - and <i>p</i> -nitrotoluene.				
		0	2.11	3.22	4.58	5.75
Setting point of TNT, found	80.80°	80.78°	79.87°	79.26°	78.70°	78.13°
" " " , calc.	—	80.80°	79.82°	79.30°	78.67°	78.13°

the products were determined. The results are recorded in Table II, the setting points being corrected. Setting points have been calculated from the equation:

$$\text{Setting point} = 80.80 - 0.465 (\text{concn. of } m\text{-nitrotoluene}) \quad (1)$$

which was derived from the data by the method of least differences. That trinitration in these experiments was substantially complete is shown by the close agreement between the setting points of products derived from *p*-nitrotoluene and 2:4-dinitrotoluene with that recorded by Rintoul (*J. Soc. Chem. Ind.*, 1916, **34**, 80).

Toluene was nitrated at various temperatures with 1.2 mols. of nitric acid in the form of a mixed acid. The nitrotoluenes, after removal of unchanged toluene, were trinitrated by the

standard method. The setting points of the trinitrotoluenes were determined and the proportions of *m*-nitrotoluene in the original nitrotoluenes were calculated from equation (1). The results,

TABLE III.

Temperature of mononitration	-30°	0°	30°	60°
Setting point of TNT	79.42°	79.09°	78.76°	78.52°
Concn. of <i>m</i> -nitrotoluene (%)	2.97	3.68	4.39	4.90

collected in Table III, show that the proportion of *m*-nitrotoluene changes almost linearly with temperature and there is no evidence that the rate of change is less for mixed acid nitrations than for nitrations in other media.

DISCUSSION.

Bradfield and Jones (*J.*, 1928, 1006) calculated, for several substitutions, the proportions of isomers formed at one temperature from the experimentally determined proportions at a second temperature by means of the Arrhenius equation, $k = nAe^{-E/RT}$, in which, for each isomer, k is the rate of formation, n is the number of equivalent substitution positions, A is a temperature-independent factor, E is the energy of activation, and T is the absolute temperature. They obtained fair agreement with experiment on the assumption that A was the same for each isomer formed in a particular reaction. The close agreement, for the proportion of *m*-nitrotoluene formed at 0° and 30°, between our results and those of Ingold *et al.*, determined by entirely different techniques, is strong evidence for the essential reliability of the experimental data. The values for *m*-nitrotoluene, calculated for other temperatures by the method of Bradfield and Jones from the data of Ingold *et al.* at 30°, are given in the left side of Table IV. They show increasing divergence from our experimental values as the temperatures depart from 30°. As these deviations are considerable and show a systematic trend they cannot be attributed to experimental error.

Better agreement between calculated and experimental results can be obtained only by assuming that the temperature-independent factors are different for the three isomers. Appropriate values for these factors can be calculated from the proportions of isomers at two temperatures, thus:

$$\text{Let } k_o = 2A_o e^{-E_o/RT}; \quad k_m = 2A_m e^{-E_m/RT}; \quad k_p = A_p e^{-E_p/RT}$$

$$\text{Then } k_o/k_m = (A_o/A_m)e^{(E_m - E_o)/RT}$$

If r_1 and r_2 are the ratios of *o*- to *m*-nitrotoluene formed at two temperatures T_1 and T_2 , then

$$2.303 \{ \log_{10} r_1 - \log_{10} (A_o/A_m) \} = (E_m - E_o)/RT_1 \quad . \quad . \quad . \quad (2)$$

$$\text{and } 2.303 \{ \log_{10} r_2 - \log_{10} (A_o/A_m) \} = (E_m - E_o)/RT_2$$

Dividing and transposing we obtain

$$\log_{10} (A_o/A_m) = (T_2 \log_{10} r_2 - T_1 \log_{10} r_1)/(T_2 - T_1) \quad . \quad . \quad . \quad (3)$$

Similarly, if s_1 and s_2 are the ratios of *p*- to *m*-nitrotoluene at T_1 and T_2 ,

$$\log_{10} (A_p/2A_m) = (T_2 \log_{10} s_2 - T_1 \log_{10} s_1)/(T_2 - T_1) \quad . \quad . \quad . \quad (4)$$

By substituting in equations (3) and (4) the ratios of isomers given by Ingold *et al.* for 0° and 30° it was found that

$$A_o = 2.90A_m \text{ and } A_p = 2.70A_m.$$

and by further calculation the proportions of isomers formed at -30° and 60°, shown in the right side of Table IV, were obtained. It is evident that much better agreement with experiment is given by the new equations.

TABLE IV.

Temp.	$A_o = A_m = A_p.$			$A_o = 2.90A_m; A_p = 2.70A_m.$		
	<i>o</i> (%).	<i>m</i> (%).	<i>p</i> (%).	<i>o</i> (%).	<i>m</i> (%).	<i>p</i> (%).
-30°	58.33	2.32	39.35	57.55	2.98	39.47
0	58.49	3.31	38.20	(58.10)	(3.70)	(38.20)
30	(58.45)	(4.40)	(37.15)	(58.45)	(4.40)	(37.15)
60	58.21	5.54	36.25	58.66	5.07	36.27

The numbers in parentheses are the experimental values on which the calculations are based.

The values of A_o and A_p are nearly equal and only small changes in the proportions of *o*- and *p*-nitrotoluene, but none in the proportions of *m*-nitrotoluene, are caused by adopting the mean value, 2.80, for both. There does not, however, appear to be any reason why, in the general case, A_o should be equal to A_p and so the separate values have been used in the calculations of Table IV.

From equation (2) and the corresponding equation for the ratio of *p*- to *m*-nitrotoluene we have obtained the following values, in cal. deg.⁻¹ mol.⁻¹, for activation energy differences :

$$E_m - E_o = 917$$

$$E_m - E_p = 1103$$

EXPERIMENTAL.

Materials.—"Nitration" toluene (National Benzole Specification No. 7, 1938) was distilled through a short column. The middle fraction, having d_{4}^{20} : 0.8710, n_{D}^{20} : 1.4963, was used. Commercial *m*-nitrotoluene was purified by fractional freezing until the maximum setting point, 16.0° (corr.), was reached. Commercial *p*-nitrotoluene and 2:4-dinitrotoluene were recrystallised from alcohol until the setting points remained unchanged at 51.6° (corr.) and 69.8° (corr.).

A stock of mononitration mixed acid was made from sulphuric acid (d 1.84, 18.8 kg.), nitric acid (d 1.42, 1.1 kg.), liquid nitrogen tetroxide (0.9 kg.), and water (4.7 kg.). Analysis of the mixture gave 71.4% H_2SO_4 , 6.35% HNO_3 , 1.75% HNO_2 , and 21.5% H_2O . Nitrous acid was added because it catalyses the nitration and prevents undue temperature fluctuations in the early stages. Dinitration and trinitration acids were made up as required for each nitration from concentrated sulphuric and nitric acids and 20% oleum that had been titrated.

Mononitration.—The all-glass apparatus was a 2-l., 3-necked, bolt-head flask fitted with paddle stirrer, reflux condenser, dropping funnel, and thermometer, the last two reaching to near the bottom. The flask was immersed in a suitable cooling bath: solid carbon dioxide and trichloroethylene for -30° and 0°, ice-water for 30°, and water at the ordinary temperature for 60°. Mixed acid (2300 g.) was placed in the nitrator and cooled to just below the reaction temperature, and toluene (150 g.) was run in, fairly rapidly at first till the intended temperature was reached and then more slowly to keep the temperature constant. After the initial warming up, the maximum variation in temperature was $\pm 1^\circ$. The addition of toluene took about 30 minutes, and the reaction was continued for a further 75 minutes except for the -30° nitration which was run for a total time of 4.5 hours. During the later stages of the reaction the bath temperature was raised gradually to keep the reaction temperature constant until, finally, outside and inside temperatures were almost equal. The reaction mixture was poured into ice-water (4 kg.), the aqueous layer was removed, and more water was added followed by ether until the organic layer was the lighter. The ethereal layer was washed with water till acid-free and dried (Na_2SO_4), and the ether was distilled off. Traces of ether and any un-nitrated toluene were removed by passing a current of air through the residue heated to 100° under reduced pressure. The nitrotoluenes were tested colorimetrically for toluene by shaking with an equal volume of a solution of sodium nitrite (2.5 g.) in 88% sulphuric acid (100 c.c.). Absence of a red colour indicates less than 0.2% of toluene (Dr. J. K. N. Jones, private communication).

Dinitration.—The apparatus was similar to that used for mononitration, except that the flask was of 1 l. capacity. It was immersed in a stirred oil-bath provided with means for heating and cooling. Mononitrotoluene (50 g.) was dissolved in 90% sulphuric acid (120 g.) in the nitrator at 50°. Mixed acid (125 g.), containing 70.0% of sulphuric acid, 21.5% of nitric acid, and 8.5% of water, was added cautiously from the dropping funnel. As soon as reaction had started the bath was cooled to about 30° and the rate of addition controlled so that all the mixed acid was added at about 50° in 30 minutes. The mixture was then rapidly heated to 70° and this temperature maintained for 1.5 hours. The product was washed thrice at 100°, each time by stirring vigorously for 15 minutes with an equal volume of water, allowing to settle for 5 minutes, and separating the aqueous layer. Solid which separated from the washings on cooling was collected and added to the main product, and the whole was dried at 100° for 3 hours.

Trinitration.—The same apparatus was used as for dinitration. The whole of the dinitration product (or 65 g. in the case of 2:4-dinitrotoluene) was dissolved in 100% sulphuric acid (220 g.) in the nitrator at 100°, the oil-bath was cooled to about 97°, and the addition of mixed acid (125 g.), containing 60% of sulphuric acid, 40% of nitric acid, and 0% of water, was started. Reaction did not begin immediately, and the addition of mixed acid was stopped after a few g. had been added until there was a noticeable rise in temperature. The bath was then cooled to about 80° and the rate of addition controlled to keep the temperature at 100°. The addition was complete in 30 to 45 minutes. Towards the end of the addition of mixed acid the bath temperature was gradually raised so that it was 95° at the end of the addition, and it was further raised to about 98° during the additional reaction time of 3.5 hours. Finally, the reaction mixture was poured on ice and kept overnight, and the solid was then collected. The trinitrotoluene was washed with water at 100°, in the same manner as the dinitrotoluene, till the acidity of the last wash, titrated to phenolphthalein, was equivalent to not more than 0.002 g. of sulphuric acid. The washed trinitrotoluene was dried for 6 hours at 100° and its setting point determined. The observed value was corrected for exposed stem.

We thank the Director-General of Scientific Research (Defence), Ministry of Supply, for permission to publish this work.

172. The Reaction of 1-Nitropropane with Formaldehyde and Ammonia.

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Products of both high and low molecular weight are formed by the interaction of 1-nitropropane, formaldehyde, and ammonia. The reaction is shown to be essentially one of the type described by Mannich, in which the nitropropane provides the necessary active hydrogen atom. Amongst the products are ring compounds of the 1:3-tetrahydro-oxazine and 1-oxa-3-azacyclooctane type.

CONSIDERABLE interest has been shown recently in the chemistry of the nitro-paraffins (see, for example, Johnson and Degenry, *J. Amer. Chem. Soc.*, 1939, **61**, 3194; Spring and Degenry, *ibid.*, 1942, **64**, 1063; Senkus, *ibid.*, 1946, **68**, 11; Johnson, *ibid.*, pp. 12, 14) and it is opportune to summarise work carried out during the past few years, but hitherto withheld from publication by reason of war-time secrecy regulations. One of the authors has previously shown that the large-scale preparation of nitro-paraffins was practicable (Urbanski, *Rocz. Chem.*, 1936, **16**, 466; 1937, **17**, 161; *Compt. rend.*, 1936, **203**, 620; 1937, **204**, 870) and has indicated their use for the production of combustible resins (Urbanski, B.P. Appln. 7681, 5th June, 1942; U.S.P. Appln. 488,456, 25th May, 1943). These resinous materials were made by the interaction of nitropropane, formaldehyde, and ammonia, and it was therefore of interest to investigate the nature of the reactions responsible for their formation. The present paper records some of the results obtained in a study of reactions which had not at that time been reported in the literature, despite the interest displayed by earlier workers (*e.g.*, Henry; Mousset; Duden, Bock, and Reid; Cerf de Mauny; Zief and Mason) in the condensation of formaldehyde, nitro-paraffins, and amines. The resins obtained from 1-nitropropane, formaldehyde, and ammonia are basic. The precise nature of the portion of high molecular weight is still uncertain, but the types of linkage are indicated by the structures of the accompanying materials of low molecular weight and by the nature of the decomposition products of the resinous materials.

The first stage in the series of reactions is the formation of 2-nitrobutanol (I) and 2-nitro-2-ethylpropane-1:3-diol (II). Since ammonia is present, together with formaldehyde, hexamethylenetetramine is also produced and this yields with (II) a molecular complex. When warmed in water this complex gives a resin similar to those obtained by the interaction of the three components. The mechanism of the reaction appears to resemble that of the Mannich reaction. From (II) and ammonia a base (III) is produced, and this then reacts with formaldehyde, giving the *N*-hydroxymethyl derivative (IV), which on cyclisation gives the *oxazine* (V). No evidence for the formation of *N*-methyl derivatives was obtained. Since only one of the hydrogen atoms in (V) can react with formaldehyde it follows that (V) cannot yield a polymer on further condensation, and its production in reactions designed to lead to resin formation is to be avoided. Under appropriate conditions, however, there may be as much as 30% of (V) present in the crude resin. It is an oil which can be separated by distillation or by precipitation of the crystalline *hydrochloride*, and yields with methyl iodide a crystalline *methiodide* (VI). The corresponding hydroxide decomposes when heated yielding nitrobutene and other decomposition products.

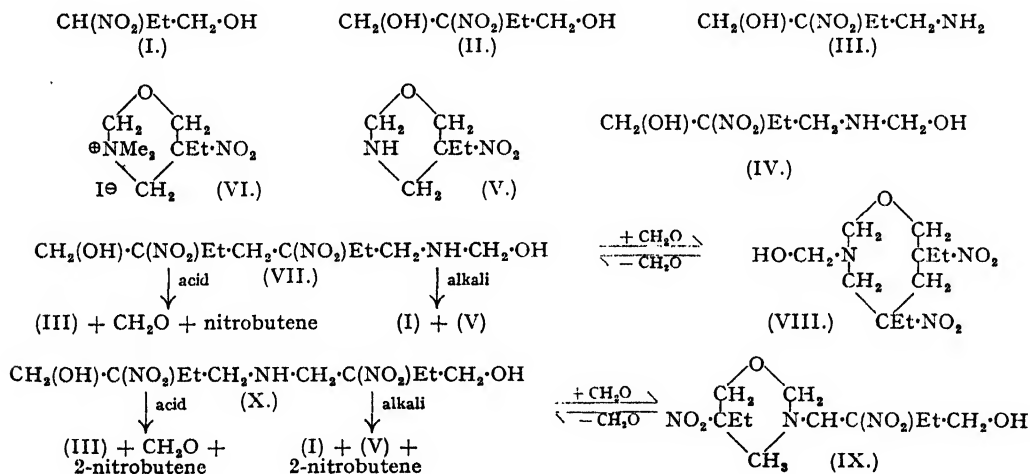
If the reaction between nitropropane, formaldehyde, and ammonia was interrupted shortly after the nitropropane had dissolved, an oily product was precipitated on cooling. It crystallised slowly, and either (VIII) or (X) was formed according to the conditions of the reaction, (VIII) being found when 1 mol. of ammonia was used per mol. of nitropropane, and (X) when 0.5 mol. of ammonia was used. (VIII) lost formaldehyde on being warmed with concentrated hydrochloric acid and gave the crystalline *hydrochloride* of (VII), and when the latter was warmed with formaldehyde it passed back into (VIII). The *hydrochloride* of (VII) gave a *picrate*; with sodium nitrite it gave an oily nitroso-compound which was reconverted into (VII) on being heated with concentrated hydrochloric acid, the presence of an imino-group being thus proved. The *hydrochloride* of (VII) when boiled in aqueous solution decomposed with the formation of the *hydrochloride* of (III), 2-nitrobutene, and formaldehyde. With aqueous sodium hydrogen carbonate it gave the crystalline base (VII) which decomposed on distillation in a vacuum giving (V) and (I). The formation of (VII) and (VIII) can be represented as an example of the Mannich reaction, and the formulæ suggested for these substances serve to explain their mode of origin and their chemical properties.

The base (IX) gives a series of reactions similar to those of (VIII). It dissolves in cold

concentrated hydrochloric acid giving a *hydrochloride* which hydrolyses in water, regenerating (IX). If (IX) is heated with dilute hydrochloric acid, 1 mol. of formaldehyde is eliminated and the *hydrochloride* of the secondary base (X) is formed. The hydrochloride of (X) when heated with aqueous formaldehyde regenerates the tertiary base (IX). The hydrochloride of (X) gave a well-defined *picrate* and an oily nitroso-compound which regenerated the hydrochloride of (X) when heated with concentrated hydrochloric acid, indicating the presence of an imino-group. The hydrochloride of (X) on treatment with aqueous sodium carbonate gave the corresponding crystalline base which decomposed when boiled with water or on distillation under reduced pressure with formation of (I), 2-nitrobutene, and (V). The hydrochloride of (X), on prolonged boiling with water, gave ammonium chloride, formaldehyde, 2-nitrobutene, and the hydrochloride of (III). The formation of (IX) and (X) and their chemical properties can most easily be explained by the mechanism shown in the accompanying scheme.

Substance (V) can be obtained from the resin by distillation under reduced pressure or by the action of hydrochloric acid, as well as by the decomposition of the bases (VII) and (X). It forms a picrate and hydrochloride and an oily nitroso-derivative. The hydrochloride when boiled with water eliminates 1 mol. of formaldehyde with formation of the hydrochloride of (III). This reaction is reversible, the hydrochloride of (III) regenerating the hydrochloride of (V) on crystallisation from propyl alcohol containing formaldehyde.

The base (III), which was unstable even at room temperature, is a primary amine, since it gives nitrogen with aqueous sodium nitrite. The action is, however, complex since the initial gentle evolution of nitrogen was followed by a violent reaction in which nitrous oxide, as well as nitrogen, was evolved and a greenish water-insoluble oil was produced.



EXPERIMENTAL.

Additive Compound $[(\text{C}_6\text{H}_{11}\text{O}_4\text{N})_3, \text{C}_6\text{H}_{12}\text{N}_4]$ of 2-Nitro-2-ethylpropane-1:3-diol and Hexamethylenetetramine.—1-Nitropropane (1 mol., 89 g.) was added to a cold mixture of 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.). The mixture was stirred at room temperature until the nitropropane disappeared (12–15 hours). After some time the aqueous solution was separated from an oily precipitate (containing 2-nitrobutanol). The addition of sodium chloride to the aqueous solution salted out an oil, which solidified in fine needles (100 g.). It was the additive compound of 2-nitro-2-ethylpropane-1:3-diol (3 mols.) and hexamethylenetetramine (1 mol.); white needles from chloroform, m. p. 117°. The additive compound is very readily soluble in water, soluble in alcohol, very slightly soluble in ether. It gave hexamethylenetetramine picrate, m. p. 179°, with picric acid, and hexamethylenetetramine hydrochloride with hydrochloric acid. It was dissociated in solution. For example, ebullimetric determination in chloroform gave M , 158 [calc. for hexamethylenetetramine, 140; for 2-nitro-2-ethylpropane-1:3-diol, 149. $(\text{C}_6\text{H}_{11}\text{O}_4\text{N})_3, \text{C}_6\text{H}_{12}\text{N}_4$ requires M , 587]. When heated it was converted into a resin.

Another method for the preparation of the additive compound consisted in mixing concentrated aqueous solutions of 2-nitro-2-ethylpropane-1:3-diol (4.47 g.) with hexamethylenetetramine (1.40 g.). The crystalline additive product (4.2 g.) was precipitated on standing [Found: CH_2O , determined by the 2:4-dinitrophenylformylhydrazine method, 30.5. $(\text{C}_6\text{H}_{11}\text{O}_4\text{N})_3, \text{C}_6\text{H}_{12}\text{N}_4$ requires CH_2O , 30.8%].

Resin A.—1-Nitropropane (1 mol., 89 g.) was heated with 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.) with stirring at 90–95° for 15–30 minutes. The reaction was then stopped by rapid cooling (pouring on ice). An oily layer containing nitro-olefins was separated

by decantation. The liquor was reheated and the temperature maintained at 90–95° for 8 hours with efficient stirring.

The resin formed a separate phase which was isolated by decantation. It was washed with hot water and dried in a partial vacuum. By evaporation of the liquor an additional quantity was obtained (yield, 110–125 g.).

Resin B.—2-Nitro-2-ethylpropane-1:3-diol (1 mol., 149 g.) was mixed with 40% formaldehyde (1 mol., 75 c.c.) and 33% ammonia ($\frac{1}{2}$ mol., 295 c.c.). The temperature was kept between 90° and 95° for 10 hours with stirring. The oily product was precipitated and, after cooling, was separated from the liquor, washed, and dried in partial vacuum (yield, 110 g.). The resin was a colourless and odourless viscid liquid.

Isolation of (V) from resins A and B. Fractionation of the resin under reduced pressure gave two fractions: (a) b. p. 140° (bath temp.)/0.01 mm., n_D^{20} 1.4720; (b) b. p. 160–180° (bath temp.)/0.01 mm., n_D^{20} 1.4880. Both fractions with methyl iodide gave a derivative, m. p. 218° (decomp.), identical with the methiodide of 5-nitro-3-methyl-5-ethyltetrahydro-1:3-oxazine (VI) described below. The liquid air trap of the distillation apparatus contained 2-nitrobutene and a blue nitroso-derivative of unknown constitution.

Isolation of (IX) by steam distillation of the resin A or B. The resin A or B (9.3 g.) was distilled in steam giving an oil (6 g.) which was mainly the base (V), since with methyl iodide it gave the crystalline methiodide (VI). The aqueous distillate was extracted with ether and then with benzene, and the combined extracts were dried (Na_2SO_4) and evaporated to a syrup (4 g.) under reduced pressure. The syrup crystallised on standing and, after tilting and recrystallising from benzene, 5-nitro-5-ethyl-3-(2-nitro-2-hydroxymethylbutyl)tetrahydro-1:3-oxazine (IX), m. p. 101°, was isolated (Found: C, 45.4; H, 7.2; N, 13.9. $\text{C}_{11}\text{H}_{21}\text{O}_6\text{N}_3$ requires C, 45.4; H, 7.2; N, 14.4%).

Preparation of the Bases (VIII) and (IX).—1-Nitropropane (1 mol., 89 g.) was mixed with 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.) and heated with stirring during 1½ hours at 90–95°. The hot solution was then poured into ice-water. The oily precipitate crystallised on standing (after ca. 2 weeks), yielding crystals of 5:7-dinitro-3-hydroxymethyl-5:7-diethyl-1-oxa-3-azacyclooctane (VIII). Recrystallised from ether and then from chloroform or from benzene-light petroleum, it gave white needles, m. p. 97° (yield, 15–20 g.). It was soluble in hot water, cold ether, alcohol, acetone, and benzene, insoluble in light petroleum. It was less soluble in chloroform than (IX). Mixed with (IX) it gave considerable depression of m. p. (70–73°) [Found: C, 45.3; H, 7.0; M (ebulliometrically in benzene), 280. $\text{C}_{11}\text{H}_{21}\text{O}_6\text{N}_3$ requires C, 45.4; H, 7.2%; M, 291].

The base (VIII) gave with cold concentrated hydrochloric acid the *hydrochloride*, m. p. 174° (Found: C, 40.1; H, 6.7; N, 12.1; Cl, 10.9. $\text{C}_{11}\text{H}_{21}\text{O}_6\text{N}_3\text{HCl}$ requires C, 40.3; H, 6.5; N, 12.8; Cl, 10.8%). This hydrochloride hydrolysed in cold water yielding the free base (VIII). On being warmed with concentrated hydrochloric acid the hydrochloride lost one molecule of formaldehyde and was converted into the *hydrochloride* of hydroxymethyl-2:4-dinitro-4-hydroxymethyl-2-ethyl-hexamylamine (VII), m. p. 179° (Found: CH_2O , 10.9. Loss of 1 mol. of CH_2O requires 10.3%). It depressed the m. p. of the hydrochloride of (VIII). This hydrochloride of (VII) was insoluble in ether, benzene, and chloroform, readily soluble in water and hot alcohol, sparingly soluble in cold alcohol. It recrystallised from alcohol in the form of small plates, m. p. 179° (decomp.) (Found: C, 38.4; H, 7.1; N, 12.4; Cl, 11.2. $\text{C}_{10}\text{H}_{21}\text{O}_6\text{N}_3\text{HCl}$ requires C, 38.0; H, 6.7; N, 13.3; Cl, 11.3%). On being heated with concentrated aqueous formaldehyde it gave an oil, which was extracted with ether; the dried extracts were evaporated in partial vacuum to a syrup, which crystallised slowly. After standing the crystals were triturated with ether and filtered. Recrystallisation from benzene gave the pure base (VIII), m. p. and mixed m. p. 97°. The hydrochloride of (VII) reacted with sodium nitrite and gave an oily nitroso-derivative soluble in ether. The latter regenerated the hydrochloride of (VII) on treatment with concentrated alcoholic hydrogen chloride.

The hydrochloride of (VII) was dissolved in alcohol and aqueous picric acid was added. The pale yellow *picrate* of (VII) was precipitated, m. p. 154° (Found: C, 38.2; H, 4.8; N, 16.4. $\text{C}_{10}\text{H}_{20}\text{O}_{13}\text{N}_3$ requires C, 37.8; H, 4.7; N, 16.5%). The picrate was unstable and could not be recrystallised from water.

The hydrochloride of (VII) (1.45 g.) was dissolved in water, and sodium hydrogen carbonate and ether were added. The syrupy base (1.33 g.) was isolated on evaporation of the solvent. The base (VII) (1.33 g.) on distillation under reduced pressure gave a fraction (0.74 g.), n_D^{20} 1.4670, b. p. 140° (bath temp.)/0.01 mm., and a still residue (0.35 g.). The volatile fraction consisted of the base (V) and 2-nitrobutanol. These were separated by dissolving the base in the calculated quantity of hydrochloric acid. The 2-nitrobutanol (I) was then extracted with ether. The base (V) was characterised by its hydrochloride, m. p. 203° (decomp.), and picrate, m. p. 153°, not depressed on admixture with an authentic specimen.

The hydrochloride of (VII) (888 mg.) was dissolved in water and the solution boiled. Decomposition occurred and formaldehyde and 2-nitrobutene distilled. The aqueous solution remaining in the flask was evaporated to dryness under reduced pressure and the residue (516 mg.) was triturated with acetone and filtered. The residue (68 mg.) was ammonium chloride. The acetone solution was evaporated to a syrup and triturated with ether; the hydrochloride of the base (III), m. p. 126° (see below), then crystallised. The aqueous distillate contained formaldehyde (Found: 9%; 1 mol. requires 9.5%) and 2-nitrobutene (characteristic odour, absorption of bromine, polymerises with alkali).

Preparation of (IX).—2-Nitro-2-ethylpropane-1:3-diol (1 mol., 149 g.) was heated with 40% formaldehyde (1 mol., 75 c.c.) and 33% ammonia ($\frac{1}{2}$ mol., 26 c.c.) at 95–96° for ca. 1½ hours. The product (IX) was isolated by pouring into ice-water. It recrystallised from ether, chloroform, or benzene-light petroleum in long needles, m. p. 101°. Yield, 50 g. [Found: C, 45.6; H, 7.0; N, 14.5; M (ebulliometrically in benzene), 285. Calc. for $\text{C}_{11}\text{H}_{21}\text{O}_6\text{N}_3$: C, 45.4; H, 7.2; N, 14.4%; M, 291].

A simple method of isolating the base (IX) from the resin B consisted in dissolving the resin in cold hydrochloric acid. The solution was poured on ice. The resinous substance precipitated was extracted

with ether, the extracts were dried and the ether was evaporated. The residue solidified into crystals of (IX), m. p. and mixed m. p. 98°.

The base (IX) reacted with cold concentrated hydrochloric acid, yielding the *hydrochloride*, m. p. 156° (Found: C, 40.4; H, 6.8; N, 12.6; Cl, 10.6. $C_{11}H_{21}O_4N_3.HCl$ requires C, 40.3; H, 6.5; N, 12.8; Cl, 10.8%). The same product was obtained by passing hydrogen chloride through a solution of the base (IX) in chloroform or carbon tetrachloride. It is insoluble in ether or chloroform, soluble in alcohol. On dissolving in water it hydrolyses giving the free base (IX), m. p. 101° (Found: C, 45.1; H, 7.3; N, 13.3%).

Hydrochloride of (X).—The base (IX) or its hydrochloride, when heated with concentrated hydrochloric acid, lost a molecule of formaldehyde and was converted into the hydrochloride of bis-2-nitro-2-hydroxymethylbutylamine (X) (Found: CH_2O , 10.3. Loss of one mol. of CH_2O requires 10.3%). The *hydrochloride* separated in plates or needles from absolute alcohol, m. p. 186° (Found: C, 38.0; H, 6.8; N, 12.7; Cl, 11.2. $C_{10}H_{19}O_4N_3.HCl$ requires C, 38.0; H, 6.7; N, 13.3; Cl, 11.3%). On warming an aqueous solution of the hydrochloride with formaldehyde solution (40%) an oil separated and was extracted with ether. The extract was dried (Na_2SO_4) and the ether removed; the base (IX) then crystallised. M. p. and mixed m. p. [with base (IX)] 99°.

The hydrochloride reacted with sodium nitrite solution giving the nitroso-derivative which separated as an oil. It was extracted with ether and the dried extracts were evaporated under reduced pressure. Concentrated hydrochloric acid reconverted it into the parent hydrochloride of (X), m. p. and mixed m. p. 186°.

Isolation of the Base (X).—The hydrochloride of (X) was dissolved in a minimum amount of water, and ether and excess of sodium hydrogen carbonate solution were added. The ethereal layer was separated and the aqueous solution extracted twice with ether. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a syrup, which crystallised on trituration with a little ether. The compound separated in a good yield as a white crystalline solid, and was recrystallised from ether–light petroleum, m. p. 54° [Found: C, 43.1; H, 7.5; (OH), 11.8. $C_{10}H_{19}O_4N_3(OH)_2$ requires C, 42.9; H, 7.5; (OH), 11.3%]. The *picrate*, after recrystallisation from water, had m. p. 148° (Found: C, 37.8; H, 5.1; N, 16.7. $C_{10}H_{19}O_4N_3$ requires C, 37.8; H, 4.7; N, 16.5%).

On boiling an aqueous solution of the base (X) two molecules of formaldehyde were liberated (Found: CH_2O , 19%. Two mols. of CH_2O require 21.5%). On distillation under reduced pressure, the base (X) (1.4 g.) gave a fraction (0.9 g.), b. p. 140° (bath temp.)/0.01 mm., n_D^{20} 1.4665, containing basic material, and a still residue (unchanged material). With alcoholic hydrogen chloride the distillate gave the crystalline hydrochloride (V), m. p. 202°. Titration with dilute hydrochloric acid showed that some of the distillate was neutral and not soluble in acid. After neutralisation the solution was therefore extracted with ether and the extracts were distilled under reduced pressure giving a fraction (0.3 g.), b. p. 120° (bath temp.)/0.01 mm., n_D^{20} 1.4438. This was 2-nitrobutanol, n_D^{20} 1.4430.

The hydrochloride of (X) (385 mg.) was dissolved in water and heated at 93° for 12 hours. The solution was then evaporated under reduced pressure and the residue (202 mg.) was triturated with acetone. The insoluble material (18 mg.) was identified as ammonium chloride. The acetone solution on evaporation gave a crystalline solid, m. p. 126°. This was the hydrochloride of (III). The aqueous distillate was extracted with ether and the formaldehyde estimated in the aqueous solution (Found: CH_2O , 7. One mol. requires 9.3%). The ethereal extract on evaporation left an oil (10 mg.) which had the reactions of 2-nitrobutene. On heating the hydrochloride of (X) with sodium hydroxide solution and then adding acid and distilling, two molecules of formaldehyde were eliminated (Found: CH_2O , 18.0. 2 mols. of CH_2O require 19.0%).

Action of Concentrated Hydrochloric Acid on Resin A.—(a) The resin dissolved in concentrated hydrochloric acid with evolution of heat. The solution was then evaporated under reduced pressure to a syrup. On standing, crystals separated. They were fractionated into hydrochlorides of (V), (VII), (X), and (IV) by the differences of their solubilities in alcohol and ether. The hydrochloride of (V) is less soluble than that of (X), which in turn is less soluble than that of (VII). The most soluble is the hydrochloride of (IV). The yields varied, (IV) being obtained in the greatest proportion (up to 30% by weight of the resin). (VII) was not obtained from Resin B.

(b) The resin was dissolved in chloroform (or alcohol) and hydrogen chloride bubbled through the solution. The gas was strongly absorbed, the colour of the solution changed from light yellow to deep orange, heat was evolved, and an evolution of formaldehyde occurred. At first a thick emulsion appeared, which then crystallised. The crystals were separated and washed with chloroform and ether. Hydrogen chloride was again passed through the filtrate and a second crop of crystals was formed and separated. This was repeated several times and finally several fractions were collected, representing the hydrochlorides of the four bases mentioned above. Yield, 80 g. from 100 g. of Resin A.

The *hydrochloride of 5-nitro-5-ethyltetrahydro-1:3-oxazine* (V) was isolated in the form of white crystals, insoluble in ether, benzene, and chloroform, readily soluble in water and alcohol, m. p. 203° (decomp.) (Found: C, 36.8; H, 6.5; N, 13.9; Cl, 17.9. $C_8H_{15}O_3N_3.HCl$ requires C, 36.7; H, 6.6; N, 14.2; Cl, 18.1%). Sodium nitrite converted it into an oily, pale yellow nitroso-derivative, soluble in hot water, insoluble in cold water, and volatile with steam. It was not decomposed on boiling with water. It distilled under reduced pressure, b. p. 130° (bath temp.)/0.01 mm., n_D^{20} 1.5000. The free base (V) was prepared from the hydrochloride (2.15 g.) by the action of sodium hydrogen carbonate and extraction with ether. Yield, 1.8 g. It is an oily liquid insoluble in water, n_D^{20} 1.4873 [Found: C, 45.4; H, 7.5; M (Rast), 162. $C_8H_{15}O_3N_3$ requires C, 45.1; H, 7.5%; M, 160]. The hydrochloride with aqueous picric acid gave a pale yellow *picrate*, m. p. 156° (Found: C, 36.8; H, 4.0; N, 18.0. $C_{12}H_{15}O_{10}N_3$ requires C, 37.0; H, 3.8; N, 18.0%).

Preparation of (VI).—The base (V) (2 g.) by the action of methyl iodide gave the crystalline *methiodide* (VI), m. p. 218° (decomp.). Yield, 1.5 g. It can also be prepared directly from the resin. The resin (3.028 g.) was dissolved in methyl iodide and the solution warmed. After 12 hours the crystals, which had separated, were triturated with acetone, filtered off, and dried. Yield, 0.7 g. It was recrystallised from methyl alcohol; m. p. 218° (decomp.) (Found: C, 30.6; H, 5.3; N, 8.4; I, 39.7;

NO_2 , 15.4. $\text{C}_8\text{H}_{17}\text{O}_3\text{N}_2\text{I}$ requires C, 30.4; H, 5.4; N, 8.9; I, 40.2; NO_2 , 14.6%. With picric acid it gave the corresponding *picrate*, m. p. 210°, after recrystallisation from water (Found: C, 40.4; H, 4.5; N, 16.8. $\text{C}_{11}\text{H}_{19}\text{O}_{10}\text{N}_2$ requires C, 40.4; H, 4.1; N, 16.8%).

An aqueous suspension of silver oxide (10 g.) converted the methiodide (1.775 g.) into the hydroxide of (VI) (1.2 g.) which, on distillation, decomposed violently, giving various liquid and gaseous products. The distillate was strongly alkaline and had a pronounced odour resembling that of methylamine. Addition of picric acid to a solution of the gaseous products absorbed in dilute hydrochloric acid gave a pale yellow *picrate* soluble in water and almost insoluble in dilute hydrochloric acid; m. p. 156°. It was identified (by mixed m. p.) as dimethylamine *picrate*. The liquid distillate contained an aldehyde or ketone, which formed a 2:4-dinitrophenylhydrazone, m. p. 166° (Found: C, 49.8; H, 4.2; N, 21.6. $\text{C}_{11}\text{H}_{14}\text{O}_4\text{N}_4$ requires C, 49.6; H, 5.3; N, 21.1%), and a base, which, with methyl iodide, gave a derivative, m. p. >300°.

Decomposition of the Hydrochloride of (V).—When the hydrochloride of (V) was boiled with water, formaldehyde (1 mol.) was evolved (Found: CH_2O , 14.1. 1 mol. of CH_2O requires 15.2%). On evaporation of the aqueous solution, the *hydrochloride* of 2-nitro-2-hydroxymethylbutylamine (III) remained. It is a crystalline solid, very soluble in alcohol, acetone, and water, sparingly soluble in ether, m. p. 126°, and is the final product of decomposition of the more complex bases (VIII), (X), (V), and (VII). No crystalline *picrate* or methiodide could be prepared. It was recrystallised from propyl alcohol; m. p. 126° (Found: C, 32.6; H, 7.0; N, 14.1; Cl, 19.5. $\text{C}_8\text{H}_{14}\text{O}_3\text{N}_2\text{HCl}$ requires C, 32.7; H, 6.8; N, 15.2; Cl, 19.3%).

The hydrochloride of (III) (1 g.) reacted with the calculated quantity of sodium nitrite dissolved in water (5 c.c.). A colourless gas was evolved, briskly at first and then more slowly; the solution became slightly milky and heat was evolved. Total volume of gas at N.T.P., 145 c.c. (Found: N, 67.6; NO, 1.8; N_2O , 24.1; CO_2 , 5.5; CO, 1.0%). This reaction occurred, if only 0.25 mol. of sodium nitrite was added. Addition of urea failed to prevent the second part of the reaction from occurring, once nitrogen had been evolved. The yellow-green oil which separated had an odour resembling that of diazomethane. The oil (0.43 g.) was extracted with ether and distilled under reduced pressure. Much decomposition occurred and a yellow acidic oil (0.1 g.) passed over, n_D^{20} 1.4700, b. p. 140° (bath temp.)/0.01 mm. (Found: C, 45.6; H, 7.4; N, 8.9%). Formaldehyde was liberated on boiling the hydrochloride of (III) with sodium hydroxide (Found: CH_2O , 11. One mol. requires CH_2O , 16.2%).

The oily base (III) was obtained by ethereal extraction of a solution of the hydrochloride made alkaline. Evaporation of dried extracts under reduced pressure gave a syrup which evolved ammonia on standing with formation of crystals. The crystals were basic, m. p. 98° depressed on admixture with (VIII) or (IX) (Found: C, 39.1; H, 7.1; N, 13.1. $\text{C}_8\text{H}_{12}\text{O}_3\text{N}_2$ requires C, 40.4; H, 7.7; N, 13.5%). This crystalline substance gave no test for primary or secondary nitro-groups. It was insoluble in ether. It gave ammonia with alkalis, whilst with concentrated alcoholic hydrogen chloride it gave formaldehyde and the hydrochloride of (III), m. p. 126°.

A sample of the mother liquor, after removal of the crystalline derivative, m. p. 98°, gave with concentrated hydrochloric acid a mixture of the hydrochloride of (V), m. p. 203° (decomp.), and the hydrochloride of (III), m. p. 126°. After removal of the base (III) by ether extraction, the mother liquors, on heating, gave an oily base with a piperidine-like odour. This was extracted with ether and the dried extracts were evaporated. The strongly alkaline oil (10% yield calculated on the weight of hydrochloride) was distilled under reduced pressure; b. p. 160°/16 mm., n_D^{20} 1.4862 (Found: C, 46.8; H, 8.1; N, 20.4. $\text{C}_{10}\text{H}_{20}\text{O}_4\text{N}_4$ requires C, 46.2; H, 7.7; N, 21.6%). The oil gave no crystalline *picrate* or methiodide. The oily methiodide contained 34.8% of iodine.

Characteristic Reaction for Bases (VIII) and (IX) and their Derivatives (VII) and (X).—The substance [(VIII), (IX), (VII), or (X)] was shaken with bromine dissolved in carbon tetrachloride; alcohol was added to produce a clear solution followed by the addition of alcoholic potassium hydroxide. The solution lost its bromine colour and became pink-red. The addition of a drop of acid deepened the colour but excess changed it to yellow. Addition of potassium hydroxide brought back the red colour. The base (V), its methiodide (VI), and the base (III) did not give this reaction.

Our thanks are due to Professor J. E. Lennard-Jones, F.R.S., Chief Scientific Officer, Ministry of Supply, for permission to publish this paper.

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[Received, October 4th, 1946.]

173. Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part I. The Interaction of Benzene with Methyl Ether.

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Methyl ether interacts with benzene at 400–500° in the presence of metal oxide catalysts to give toluene and polymethylbenzenes. The most effective catalysts are of the synthetic aluminosilicate type. The reaction has been investigated under various conditions of temperature, contact time, etc.; the gaseous products have been determined. Under the optimum conditions for the reaction, 12–15% (moles) of toluene per pass is formed, or 35–50% calculated on the benzene consumed; the total methylation (on benzene consumed) is about 70%. Wastage of the reactants is low.

The results obtained are compared with those of previous work, and the nature of the reaction is briefly discussed.

THE various known methods for alkylating aromatic hydrocarbons in solution, *e.g.*, the Friedel-Crafts reaction and its modifications, have been thoroughly investigated (see, *e.g.*, Calloway, *Chem. Reviews*, 1935, 17, 327; Linstead, *Ann. Reports*, 1937, 34, 254); they have been very widely applied, and their mechanisms have been elucidated. In recent years, several processes for the production of certain alkylbenzenes in the gas phase have been reported, but gas-phase alkylation as a general method has not been investigated nearly so extensively as the corresponding reaction in solution, and available data on the reactions which have been studied are limited in scope.

The catalytic ethylation of benzene by means of ethanol or ethylene in the gas phase is a reaction now widely used in the United States in the manufacture of ethylbenzene (and hence styrene) for the production of plastics and synthetic rubber (Anon., *Oil and Gas J.*, 1942, 41, No. 13, 14). Kieselguhr, impregnated with phosphoric acid, and aluminium silicates are suitable catalysts (see, *e.g.*, Standard Oil Co., U.S.P.P. 2,238,594, 2,390,211, 2,067,764; Ipatieff and Schmerling, *Ind. Eng. Chem.*, 1946, 38, 400; Pardee and Dodge, *ibid.*, 1943, 36, 273). Other olefins, such as propene and the butenes, or alcohols or ethers which can give rise to them, have been used in similar processes (see Universal Oil Co., B.P. 464,752, 1935; Ipatieff, Pines, and Schaad, *J. Amer. Chem. Soc.*, 1944, 66, 816).

The particular case of methylation is of interest, since the reaction cannot proceed by way of an olefin. Methanol, methyl ether, and methyl chloride have been used as methylating agents in gas-phase reactions. For instance, Jenkins (B.Sc. Thesis, Oxford, 1940) observed that when benzene and methanol were passed over bauxite heated to 400°, about 2% of toluene was formed, together with much methyl ether and water. (Other published work is reviewed, and considered in relation to the present work, below, under "Discussion.") It is well known that methanol is rapidly converted into methyl ether and water in the presence of certain metal oxide catalysts: $2\text{CH}_3\text{OH} = (\text{CH}_3)_2\text{O} + \text{H}_2\text{O}$ (see, *e.g.*, Adkins and Perkins, *J. Physical Chem.*, 1928, 32, 221). Hence, when benzene and methanol vapours are led over a catalyst, it is uncertain whether the alcohol or the ether is the actual reactant.

Our experiments confirm that methyl ether interacts with benzene in the presence of catalysts to give methylbenzenes, and show that water is one of the reaction products. We find that, under the conditions we have employed, the ether is a more effective methylating agent than the alcohol. We obtain yields of toluene comparable with those claimed by previous workers (see p. 933), *viz.*, 15% (moles) per pass, and 35–50% on the benzene consumed, the total methylation (on benzene consumed) being about 70%. (Here and throughout the paper, all yields are given as moles %.) The wastage of methyl ether is 10–15% per pass.

In the present communication we present a study of the interaction of benzene and methyl ether. A number of catalysts have been examined, and the reaction investigated under various conditions of temperature, contact time, etc. The gaseous products of the reaction have been determined. Subsequent communications will describe the isomeric composition of the polymethyl derivatives formed in the methylation of benzene and its homologues, and also the methylation of thiophene and pyridine. Certain catalytic rearrangements and cracking reactions undergone by the aromatic compounds will also be reported later.

EXPERIMENTAL.

The vapours of benzene and methyl ether were led at known and constant rates through an electrically heated horizontal Pyrex tube containing the catalyst. The liquid products were analysed by fractional distillation in a Podbielniak still, and gaseous products were collected and also analysed.

1. *Materials.*—*Benzene.* "AnalaR" Benzene was purified by crystallisation, and distillation from phosphoric oxide; n_D^{20} 1.5007–1.5010, m. p. 5.4°.

Methyl ether. This was prepared by passing methanol over alumina at 375°, and collected in sulphuric acid. The ether was regenerated by running the sulphuric acid solution into water, and was dried, liquefied by cooling, and poured into a cylinder while cold. A needle valve was then screwed into the cylinder.

Catalysts. Three naturally-occurring materials have been used as catalysts, *viz.*, two specimens of bauxite, and a Scottish bauxitic clay. Two further catalysts were made by extraction of the bauxitic clay with acids to reduce, first, the alumina (Silica "O"), and secondly, the titania content (Silica "T"). The analyses were as shown in Table I.

Alumina A. Activated alumina, supplied by Peter Spence, Ltd.

Alumina B. "Special activated alumina", supplied by Peter Spence, Ltd.

Alumina C. Prepared by running 8% sodium hydroxide solution into 36% aluminium nitrate solution at 50–55°; 8/14 mesh.

Alumina D. Prepared by precipitation of aluminium nitrate solution with ammonia, by the method of Adkins and Krause (*J. Amer. Chem. Soc.*, 1922, 44, 385).

Alumina E. Supplied by I.C.I. Ltd.; screened 10/18 mesh.

Ferric oxide. Prepared in the same way as Alumina C.

TABLE I.

	Bauxite A. ¹	Bauxite B. ²	Natural aluminosilicate. ³	Silica- "O". ³	Silica "T". ³
Loss on ignition, %	22.7	21.7	7	0.78	0.92
Al ₂ O ₃ , %	35.6	67.9	41—42	7.44	2.11
SiO ₂ , %	30.9	0.96	48	85.95	92.06
Fe ₂ O ₃ , %	6.9	7.17	1	0.27	0.27
TiO ₂ , %	4.3	2.83	1—2	4.04	2.52

¹ Traces of Cr, Mn, and SO₄²⁻; analysis made by I.C.I. Ltd.

² Trace of Mg; analysis by Dr. Hartley, Inorganic Chemistry Laboratory, Oxford.

³ The materials and their analyses were supplied by Messrs. Peter Spence Ltd.; all three had been heated to 500° before analysis.

Titania gel. Titanium tetrachloride was run slowly into excess of 10% ammonia.

Silica gel, basic aluminium phosphate, boron phosphate, and thoria gel. Supplied by I.C.I. Ltd.

Chromic oxide gel. A dilute solution of chromic nitrate was precipitated at 78—84° with 17% ammonia solution.

Zinc oxide gel. Zinc chloride solution was precipitated with sodium hydroxide solution (see Adkins and Millington, *J. Amer. Chem. Soc.*, 1929, **51**, 2452).

Nickel-alumina. A method of Balandin and Rubinstein (*Z. physikal. Chem.*, 1935, **B**, **31**, 793) was used. Sufficient 10% sodium hydroxide was run into 0.25M-aluminium nitrate solution just to redissolve the precipitate first formed. An equivalent quantity of nickel nitrate in 0.5M-solution was run in with stirring. After being washed, filtered off, and dried, the product was reduced in hydrogen at 320—340°.

Mixed oxide-silica catalysts. The following mixtures of silica with other oxides were prepared by Dr. W. Cule Davies, of Peter Spence Ltd., by precipitation of sodium silicate solution with an appropriate salt: Al₂O₃-SiO₂, 3 : 1, 1 : 1, 1 : 2, 1 : 4; Cr₂O₃-SiO₂, 1 : 2; TiO₂-SiO₂, 1 : 2; BeO-SiO₂, 1 : 1.

Except where otherwise stated, all materials were screened 4/8 mesh.

2. *Apparatus.*—The rate of flow of methyl ether was measured with a flow-meter; this was calibrated for rates of flow of 0—40 g. (0—20 l.) per hour by absorption in concentrated sulphuric acid and weighing the methyl ether passed in a known time for a known deflection of the flow-meter. The gas was freed from water, carbon dioxide, and methanol by passing through a long tube packed with soda-lime and calcium chloride.

The benzene was vaporised in a Dewar vessel by heating electrically with a small element immersed in the liquid (principle suggested by Adkins, *J. Amer. Chem. Soc.*, 1922, **44**, 2175). Since the insulation provided by a Dewar vessel is not perfect, the apparatus had to be calibrated directly. Benzene could be vaporised conveniently at rates of 15—100 g. per hour.

The vapours were mixed, preheated, and injected into the catalyst chamber, a Pyrex tube 2.9 cm. in diameter; the catalyst column in the evenly heated section of the furnace was 84 cm. long. The tube was heated in an electric furnace whose temperature could be kept constant $\pm 2^\circ$ by suitable adjustment of a rheostat. The temperature was measured with a thermocouple and millivoltmeter. The charge of catalyst was 200—450 g., depending on its bulk density.

The liquid reaction products were collected, separated from water, dried and analysed by fractional distillation.

Podbielniak still used in analysis. Analyses of the liquid products of reaction were made by means of a Podbielniak-type still (column of 0.55 cm. internal diameter); this enabled benzene and its homologues to be separated without difficulty. For instance, 1.5 c.c. of toluene in 20 c.c. of benzene could be determined with a maximum uncertainty of 0.1 c.c., and larger samples were analysed with corresponding or greater accuracy.

Gas analyses. These were performed with the standard Bone and Wheeler apparatus. As absorbents, 86% H₂SO₄, 20% KOH, 20% oleum, and alkaline pyrogallol were used for methyl ether, CO₂, C₂H₄, and O₂ respectively, H₂ and CO were determined by combustion in a copper oxide pipette, and paraffins by explosion.

3. *Method of Working.*—Before use, each catalyst was heated to 500° in a stream of nitrogen; it was then repacked in the tube to ensure that no appreciable space was left above the solid catalyst. Benzene and methyl ether were passed over the heated catalyst at known rates and for a known length of time. The liquid products (50—100 c.c.) were collected, separated from water, and analysed by fractional distillation. The gaseous products were led through a trap cooled in a freezing mixture of ice and salt (to remove benzene vapour) before collection.

It was found that the activity of the catalysts fell with continued use; hence they were re-activated as necessary by heating in a stream of oxygen for 1—2 hours at 500° (oxides such as Cr₂O₃ which are oxidizable were not so treated).

Results.—1. *Search for active catalysts.* As a primary step, methyl ether was passed with benzene over a heated sample of the specimen of bauxite used by Jenkins (*loc. cit.*) in his experiments with benzene and methanol. The yield of toluene was small (3—5% per pass), although greater than that obtained by Jenkins. Therefore a search for more active catalysts was undertaken.

(i) A preliminary survey of the effect of catalysts on the rate of production of methylbenzenes was carried out in an apparatus of the type used for studying the kinetics of gaseous reactions. Methyl ether was found to be strongly adsorbed on the catalysts examined, and to undergo faster and more complex decomposition than the homogeneous reactions in the gas phase (cf. Hinshelwood and Askey, *Proc. Roy. Soc.*, 1927, **A**, **115**, 215; Staveley and Hinshelwood, *J.*, 1937, 1568). By comparing the pressure-time curves, and the analyses of the gaseous products, obtained when pure methyl ether, and ether plus benzene, were admitted to the apparatus, a qualitative series of catalytic activities was obtained. Alumina B, C, D, and E, ferric oxide, titania, silica, thoria, chromic oxide, zinc oxide, and nickel-alumina

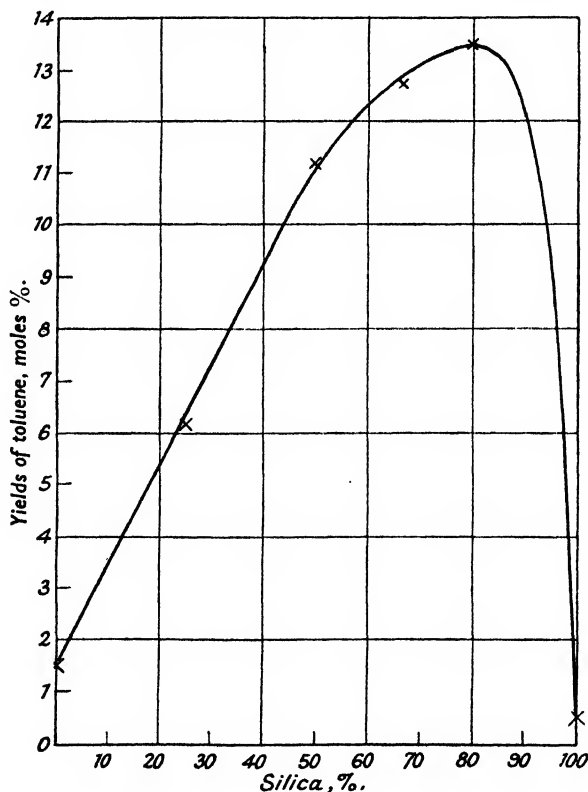
appeared to be ineffective as catalysts. Alumina A, basic aluminium phosphate, and boron phosphate were deemed worthy of further study.

(ii) The search was continued by the flow method described above. In all cases the criterion of the activity of a catalyst was the yield of toluene (moles of toluene as percentage of moles of benzene passed) under the following standard conditions: Vol. of packed catalyst space, 600 c.c.; temp. 450°; rate of flow of benzene, 42 g. per hour; of methyl ether, 12 g. per hour; molar ratio, benzene to ether, 1:8; contact time of benzene 30 secs.; space rate of flow of benzene about 0.15 c.c. of liquid per hour per volume of catalyst. It may be noted that the yield of polymethylbenzene was in all cases less than that of toluene. The average yields under the above conditions are given below in Table II.

TABLE II.

Catalyst.	Yield of toluene (moles %).	Catalyst.	Yield of toluene (moles %).
Bauxite A	4.0	Alumina-silica 1 : 1	11.3
Bauxite B	0.5	" " 1 : 2	13.0
Alumina A	1.5	" " 1 : 4	13.6
Silica	0.5	Chromic oxide-silica	1.7
Boron phosphate	2.0	Titania-silica	5.2
Basic aluminium phosphate	2.7	Beryllia-silica	6.7
Bauxitic clay	4.5	Silica " O "	6.5
Alumina-silica 3 : 1	6.2	Silica " T "	0.8

The plot of yield of toluene against percentage of silica for the alumina-silica mixtures is reproduced in the figure.



Yields of toluene as a function of composition of alumina-silica mixtures.

The mixtures of silica and other oxides are evidently the most effective catalysts, and the 1 : 4 mixture was adopted for all further work.

3. *More detailed investigation of the reaction on alumina-silica catalyst (1 : 4).* Some experiments were made to determine the effect on the reaction between benzene and methyl ether of varying the reaction conditions. The alumina-silica (1 : 4) catalyst was used throughout.

(i) *Rate of flow of reactants.* The yield of toluene was surprisingly insensitive to variations in the time of contact with the catalyst (see runs 179, 178, 181 in Table III),

TABLE III.

Catalyst: Alumina-silica 1:4.

Run.	Temp.	Rate of flow (g./hr.).		Molar ratio, $C_6H_6/C_6H_{10}O$.	Percentage yields of		
		Benzene.	Ether.		Toluene.	Xylene.	Higher.
179	450°	15.5	7.5	1.1	12.1	4.3	4.1
178	450	42.0	22.9	1.1	12.3	3.8	3.0
181	450	80.0	47.5	1.1	11.0	3.3	3.8
174	450	42.0	7.2	3.4	8.5	—	—
176	450	42.0	15.5	1.6	13.2	4.8	2.7
184	450	42.0	30.0	0.83	13.0	3.3	6.1
186	400	38.5	22.9	1.0	9.1	2.0	3.5
187	400	38.5	12.5	1.9	8.4	1.9	2.9
192*	500	38.5	12.0	1.9	17.3	4.9	2.2
193	500	25.5	22.7	0.65	15.0	5.9	3.2
194	500	27.2	12.0	1.3	15.5	4.0	3.2

* First use of new batch of catalyst.

(ii) Ratio of benzene to ether. It is seen from Table III (runs 174, 176, 184; also 186, 187) that when the rate of flow of benzene is kept constant, an increase in the molar ratio benzene: ether causes only a slight decrease in the yield of methylated products.

(iii) Temperature. The results of experiments at 400° and 500° are given in Table III (runs 186, 187, 192—194). The yields are not markedly temperature-dependent. Experiments over a wider range of temperatures were performed with Bauxite A as catalyst (300—500°). The yield of toluene fell off from 4.0 at 450° to 2.4 at 400°, 1.6 at 350°, and 0.6 at 300°.

(iv) Wastage of reactants, and yields calculated on benzene consumed. In Table IV some representative figures for the recovery of unchanged benzene are given in col. 3; in col. 4, 5, and 6 are given the yields of methylated products calculated on the benzene consumed, *i.e.*, input of benzene less recovered benzene. The total methylation is given in col. 7, the total methylation calculated on the input of benzene in col. 8, and in col. 9 is shown the loss of benzene, *i.e.*, the defect from 100% of the sum of the total methylation (calculated on input) and the benzene recovered.

TABLE IV.

1. Run.	2. Temp.	3. C_6H_6 recovered, %.	4. Percentage yields of			7. Total methyln. on C_6H_6 recovered.	8. Total methyln. on C_6H_6 input.	9. % Loss of C_6H_6 .
			Toluene.	Xylene.	Higher			
172	450°	68	46.3	15.4	9.0	70.7	22.5	9.5
176	450	71	45.3	16.6	9.4	71.3	20.7	8.3
186	400	68	28.1	6.4	10.9	45.4	14.6	17.4
189	500	73	51.1	13.7	5.2	70.0	19.2	7.8
192	500	65	49.6	14.0	6.2	69.8	24.4	10.6

The wastage of methyl ether per run is estimated below.

4. *Some general observations on the reaction of benzene with methyl ether.* The products of reaction were in all cases pale yellow or orange liquids with a green fluorescence, and contained water (see below). The polymethylbenzenes collected from a large number of runs were found on distillation to contain a small quantity of material boiling above hexamethylbenzene (the polymethylbenzenes will be dealt with more fully in a subsequent communication); this amounted to about 1% of the yield of methylated products, and was possibly a mixture of diphenyl derivatives. Apart from this (and water), no other products than methylbenzenes were detected, except in the methylation of benzene on the beryllia-silica catalyst when methanol was formed, in amount roughly equivalent to the toluene produced. The methanol was separated as its azeotrope with benzene, and characterised by means of its 3:5-dinitrobenzoate (m. p. 107°). A certain amount of carbon deposition was observed on all the catalysts.

As already noted, catalysts were reactivated when necessary by heating to 500° in a stream of oxygen for 1—2 hours. The activity of the most active catalyst, alumina-silica (1:4), decreased appreciably with continued use, in spite of reactivation; for instance, comparable figures for total methylation (at 500°) are: on a fresh batch of the material, 24%; on one which had been used in 20 previous runs (*i.e.*, ca. 800 g. of benzene had passed over it), 19%.

5. *Use of methanol as a methylating agent.* In view of the fact that other workers have used methanol as a methylating agent, it was thought of interest to compare its reaction with benzene with that of methyl ether with benzene, under the same conditions. It was found that methanol is a much less effective methylating agent than the ether; *e.g.*, when basic aluminium phosphate and the alumina-silica (1:4) were used as catalysts at 450°, the yields of toluene were $\frac{1}{2}$ % and 1% respectively when methanol was the reactant, and 2.7% and 13.0% with methyl ether, for corresponding rates of flow of the reactants. Water and methyl ether were by-products of the reaction of methanol and benzene.

6. *Decomposition of methyl ether.* It was of obvious interest to determine the fate in a methylation experiment of the methyl ether which does not react with benzene. The gaseous products of reaction consist mainly of hydrogen, carbon monoxide, and paraffin, but whereas in the homogeneous decomposition of the ether these products are formed in nearly equal amounts (Hinshelwood and Askey, *loc. cit.*), in

the heterogeneous reaction (in the presence or absence of benzene) they are formed in widely differing proportions in the presence of different catalysts (see Table V). Water was always found in the products of the reaction of benzene with methyl ether, and of the decomposition of the ether alone. When the alumina-silica mixtures were used as catalysts, the ratio of total weight of ether passed to water produced was more or less constant: 1 mole of ether gave about 0.8—1.0 mole of water. Water is therefore one of the products of decomposition of methyl ether on these catalysts. In no case of the surface reaction studied here has it been possible to write a simple stoichiometric equation between methyl ether and its products of decomposition. Therefore it has not been possible to calculate accurately the wastage of ether in a methylation run from the amount and composition of the gaseous products of reaction. However, from measurements of the volume of gas produced in a known time, during the course of an experiment, and its analysis, the amount of ether decomposed in passage over the catalyst was calculated, on the assumption that the decomposition is accompanied by a trebling of the initial volume. Thus, in the course of a methylation experiment with the alumina-silica (1 : 4) catalyst at 450°, about 10—15% of the ether is decomposed to permanent gases and water; if ether alone is passed over the catalyst the figure is about 20%.

In Table V are presented some representative analyses of the gaseous products resulting from experiments in which (a) methyl ether alone, (b) methanol alone, and (c) benzene plus methyl ether were passed

TABLE V.

Analysis of the gaseous products of reaction.

(All the figures are on a nitrogen-free, ether-free basis, except those for ether itself, which are on a nitrogen-free basis; the analyses are percentage volumes.)

Catalyst.	Temp.	Me ₂ O.	CO ₂ .	C ₂ H ₄ .	H ₂ .	CO.	C _n H _{2n+2} .	n.
Bauxite A	480°	1.3	5.0	0.4	36.0	24.8	34.7	1.2
" *	480	2.9	3.4	0.4	32.6	26.6	33.8	1.2
Alumina A	440	8.4	0.7	13.3	33.4	18.9	35.0	1.3
" *	440	20.7	2.0	5.3	35.3	22.2	30.8	1.4
Basic Al phosphate	440	16.1	3.3	4.4	8.8	16.8	66.7	1.4
" " †	440	2.7	0.2	1.5	64.7	1.4	32.2	1.25
" " *	440	33.5	16.6	1.9	21.8	25.1	34.6	1.6
" " †	440	27.9	4.2	8.4	24.2	29.2	33.6	1.25
Boron phosphate	480	13.6	3.4	5.1	0	8.3	83.3	1.1
" " †	480	3.6	2.3	1.6	0	12.0	84.1	1.4
Thoria	440	2.8	0.8	0.7	70.0	25.1	3.5	1.9
" †	440	0.2	0.7	0.3	76.6	21.2	1.1	—
Bauxitic clay	450	79.7	7.7	3.6	19.9	13.8	55.1	1.5
" *	450	68.5	16.7	5.9	14.7	11.8	52.0	1.45
Al ₂ O ₃ -SiO ₂ (1 : 4)	450	0.8	1.0	1.2	4.2	20.4	73.3	1.1
" "	450	3.2	1.3	2.3	2.7	14.0	7.90	1.1
" " *	500	0.6	1.1	0.7	15.4	9.5	73.4	1.1
" " *	500	0.5	0.6	3.0	8.5	7.7	80.0	1.0
BeO-SiO ₂	450	67.3	2.6	3.2	10.7	17.2	66.0	1.1

* Products of reaction of benzene and methyl ether.

† Decomposition of methanol.

‡ Products of reaction of benzene and methanol.

Where no sign appears, the figures refer to the decomposition of methyl ether.

over various catalysts. In addition to the observations quoted above, the following points may be noted: (1) The average carbon number, *n*, of the paraffins was nearly always greater than unity. (2) In most cases, the gases had nearly the same composition when (a) methyl ether alone or (b) methyl ether plus benzene were passed over the same catalyst. (3) A comparison of the decompositions of methanol and methyl ether is interesting: when these substances decompose on the surface of boron phosphate, the gaseous products have nearly the same composition in each case, and the same is true of several other materials which are known to catalyse the conversion of methanol into methyl ether (*e.g.*, alumina, titania, thoria, bauxite, chromic oxide; see Sabatier and Mailhe, *Ann. Chim. Phys.*, 1910, 20, 298).

DISCUSSION.

The production of toluene by reaction of methanol or methyl ether with benzene at atmospheric pressure is claimed in B.P. 574,738 (Standard Oil Development Co., application dated April 1942; complete specification accepted January 1946 *). The reactants are passed at 300—460° over a catalyst of the "solid" phosphoric acid type, which is prepared by treating a siliceous material (such as clay, kieselguhr, or a synthetic alumina-silica mixture) with a phosphoric acid. Yields of up to 50 moles of toluene per mole of benzene consumed are claimed, though it is not clear how these are calculated from the figures presented. The yields of toluene

* It appears that the work which led to this and the following patent specification was being carried out simultaneously with the work described here, which, with that to be described in subsequent papers of the series, was performed in 1940—1944 and was submitted in 1944 in a thesis for the degree of D.Phil., Oxford, by one of us (P. H. G.).

obtained by us are of comparable magnitude. Our optimum temperature range, 450—500°, is higher than that quoted for the above process (*i.e.*, 325—425°). Methanol is a more effective methylating agent in the Standard Oil Co. process than methyl ether; comparable figures are (for a reaction temperature of 354—358°): 12.2% (moles) of toluene per pass for methanol, and 7.9% for methyl ether as reactant (we obtained 1% and 11.0% respectively at 450° for approximately the same space rate of flow, using the alumina-silica catalyst).

A similar process has been patented by the Gas Light and Coke Co. (B.P. 541,534, application dated 1942), which involves bringing a (4 : 1 molecular) mixture of benzene and methanol at 250—600° (480°) and 100—300 atm. into contact with a phosphoric acid (H_3PO_4) or a metal (magnesium) phosphate alone or on an inert support, *e.g.*, coke, charcoal, siliceous material. The yield of toluene claimed is 14% by volume (12.2 moles %) on benzene passed. A further patent of the same company (B.P. 577,314, application dated March 1942, complete specification accepted May 1946) covers the use of methyl ether in a similar process, virtually the same reaction conditions being employed; the yield of toluene claimed is 18% per pass (15.5% moles), xylenes 4%, polymethylbenzenes 4%, *i.e.*, methyl ether is a more effective methylating agent than methanol in this process. The process uses roughly the same reaction temperatures as ours and gives similar yields, but requires the application of 100—300 atm. pressure.

Cullinane and Chard (*J.*, 1945, 821) have described the interaction of phenol and methanol on alumina at 200—375° to give anisole, homologues of phenol, and hexamethylbenzene.

Kutz and Corson (*J. Amer. Chem. Soc.*, 1945, 67, 1312) have described the methylation of benzene, toluene, and naphthalene with methyl chloride at 400° over alumina, alumina-silica mixtures, and other materials. In the reaction of benzene on alumina they claim yields of 8—15% (moles) of toluene, which are similar to ours obtained by the use of methyl ether. For their reaction, they find alumina a more active catalyst than the synthetic aluminosilicates.

It is noteworthy that in all these processes for the methylation of benzene, monomethylation predominates, and our work confirms this. This characteristic of the gas-phase reaction is in marked contrast to the property of the Friedel-Crafts method, *viz.*, that the monomethyl product is always accompanied by large quantities of polymethyl derivatives. In fact, the latter method is of little value for preparing monoalkylbenzenes.

Comparison of Methanol and Methyl Ether.—It is of interest to enquire whether, when toluene is produced by passing methanol and benzene over a catalyst, the methanol reacts directly, or first gives methyl ether, which then reacts with benzene. Previous workers (see above; and Cullinane and Chard, *loc. cit.*) do not appear to have envisaged the latter possibility. Our results show that, at least under the conditions we have used, methanol very probably acts as a methylating agent only by virtue of its ready conversion into methyl ether. Thus, we find that the ether gives a much better yield of toluene in reaction with benzene than does methanol. On many catalysts the decomposition products of methanol, produced under the same conditions as obtain in the course of a methylation, have very nearly the same composition as those of methyl ether on the same catalyst; this must mean that the alcohol is rapidly converted into the ether and water, and the ether then decomposes to the final products. In this connection, it may be mentioned that McKee and Burke (*Ind. Eng. Chem.*, 1923, 15, 793) have shown that the equilibrium between methanol, methyl ether, and water is rapidly achieved at 350° on alumina, and have determined the equilibrium constant at that temperature.

It may be noted that at the temperatures used in methylation experiments, the equilibrium constant of the methanol-methyl ether conversion is of the order of magnitude unity. Given (*J.*, 1943, 589) has obtained :

$$2CH_3\cdot OH (v) = (CH_3)_2O + H_2O (v) : \log_e K_p = 7300/RT - 4.8$$

The values of $\log_{10} K_p$ at various relevant temperatures, calculated from this equation, are given in Table VI. The equilibrium constant is actually unity at 761° K. (488° C.). Of course, if the

TABLE VI.
Equilibrium constants of methanol-methyl ether conversion.

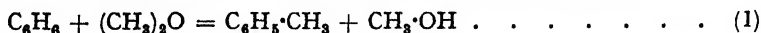
Temp., ° K.	300	400	500	600	700	800	900	1000
$\log_{10} K_p$	3.21	19.8	1.09	0.56	0.19	-0.10	-0.32	-0.50

methyl ether produced decomposes, or reacts with benzene, the equilibrium will be shifted by a mass-action effect.

The Metal Oxide-Silica Catalysts.—Our experiments show that the mixed oxide catalysts are all more active than any of the pure oxides examined and that the catalytic activity of the

alumina-silica mixtures varies in an apparently rational way with composition (see Fig.). One would expect there to be some characteristic physical property which distinguishes these materials from the pure oxides, and which varies in a rational manner in a series of mixtures with composition; it is not immediately apparent what that property is. It may be noted that synthetic alumina-silica mixtures have found wide application recently in catalysing many reactions of hydrocarbons, such as polymerisation, isomerisation, and cracking (see, e.g., Nikolaeva and Frost, *Bull. Acad. Sci. U.R.S.S., Cl. Sci. Tech.*, 1944, 536; Thomas, *Ind. Eng. Chem.*, 1945, 37, 543).

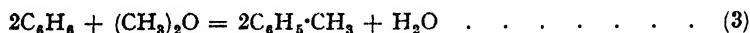
Nature of the Reaction between Methyl Ether and Benzene.—The simplest equation which can be written to represent the reaction of benzene and methyl ether to give toluene is



presumably followed by



These can be combined into



As stated above, the only reaction products we have detected are methylbenzenes, water, and permanent gases. The gases have virtually the same composition as the decomposition products of methyl ether determined in separate experiments on the same catalyst. It is logical to assume, therefore, that the gases produced in the reaction of benzene and methyl ether are not primary products, but result only from secondary cracking of the ether.

With one exception (the beryllia-silica mixture), we have never found methanol in the reaction products of benzene and methyl ether; in view of the known readiness of reaction (2) this is not surprising. Thus the available analytical data are in accordance with the suggestion that reaction (1) represents the course of the interaction of benzene and methyl ether, but are not sufficient to establish this unequivocally.

Thermodynamic Considerations.—It was thought of interest to determine how nearly the yields of toluene so far obtained approach the theoretical equilibrium values. We have calculated the thermodynamic equilibria in both reactions (1) and (3) above.

The change in heat capacity in both reactions is small over the relevant range of temperatures, and so the heats of reaction were taken as independent of temperature. Considering all the reactants in the gaseous state, we obtain:

$$\begin{aligned} \text{Reaction (1): } \Delta H^\circ_{298.16} &= -10.23 \text{ kcal.}; \Delta G^\circ_{298.16} = -11.68 \text{ kcal.} \\ &\text{and } \Delta G^\circ = -10,230 - 4.86T \quad (4) \end{aligned}$$

$$\begin{aligned} \text{Reaction (3): } \Delta H^\circ_{298.16} &= -27.89 \text{ kcal.}; \Delta G^\circ_{298.16} = -29.525 \text{ kcal.} \\ &\text{and } \Delta G^\circ = -27,890 - 5.48T \quad (5) \end{aligned}$$

We see from equations (4) and (5) that the free-energy changes of both reactions are always negative. Values of the equilibrium constants are given in Table VII.

TABLE VII.

$T^\circ \text{K.}$	298.16.	500.	723.	1000.
Reaction (1) $\log_{10} K_p$	18.2	5.50	4.13	3.28
Reaction (3) $\log_{10} K_p$	21.5	13.31	9.57	6.25

We conclude from the data here presented that, thermodynamically, the conversion of benzene into toluene by reaction with methyl ether approaches 100%, and is far larger than that so far observed experimentally. (The data employed were obtained from Pitzer and Scott, *J. Amer. Chem. Soc.*, 1943, 65, 803; Prosen, Gilmont, and Rossini, *J. Res. Nat. Bur. Stand.*, 1945, 34, 65; Bichowsky and Rossini, "Thermochemistry of some Chemical Substances"; Crawford, *J. Chem. Physics*, 1943, 8, 526; Given, *loc. cit.*).

The authors wish to express their gratitude to Dr. E. H. Rodd and Dr. Green of I.C.I. (Dyestuffs) Ltd. for helpful discussions and gifts of materials for use as catalysts; Dr. W. Cule Davies and Messrs. Peter Spence Ltd. for the preparation of the metal oxide-silica catalysts, which was specially undertaken; and the Department of Scientific and Industrial Research for grants to one of them (P. H. G.).

174. Curare Alkaloids. Part VI. Alkaloids from *Chondrodendron tomentosum* R. and P.

By HAROLD KING.

d-Tubocurarine chloride is of value in anæsthesia. The discovery of its botanical origin to ensure future supplies is therefore of importance. *Chondrodendron tomentosum* Ruiz and Pavon has been examined and found to yield *l*-curine and *l*-tubocurarine chloride. Dutcher (*J. Amer. Chem. Soc.*, 1946, **68**, 419) has also examined tube-curare prepared on the Upper Amazon from *Ch. tomentosum* but found *d*-tubocurarine chloride, *l*-curine, and other non-quaternary bases. It is possible that undifferentiated species are covered by the name *Ch. tomentosum*.

IN 1935 it was shown (King, *J.*, 1931) that the active principle of tube-curare of native origin was crystalline *d*-tubocurarine chloride. The botanical origin of the poison was not known, but the view was expressed that the genus *Chondrodendron* was probably involved. It was also known, from museum specimens and from the exploratory journeys of Poeppig in the early years of the last century, that tube-curare came from the upper waters of the Amazon in Peru. Through the kind co-operation of Mr. J. W. Massey of the British Consulate at Iquitos in Peru, I received in 1939 a quantity of the liane, "amphi huasca" (amphi = poison, huasca = rope), used by the Indians near Tarapoto in the preparation of curare, which was collected by the late Guillermo Klug. At the same time I also received ample specimens of the leaves of the same liane, and these were identified by Mr. N. Y. Sandwith, M.A., of The Herbarium, Kew, as being indistinguishable from the leaves of *Ch. tomentosum* R. and P. They agreed perfectly with leaves (herbarium sheet No. 4474) collected by Spruce at Tarapoto in 1856 and identified as *Ch. tomentosum* by Moldenke (Krukoff and Moldenke, *Brittonia*, 1938, **3**, 16).

The powdered stem was extracted with dilute tartaric acid; a sample of the neutralised extract had a true curare action when tested on the frog. The extract was worked up for non-quaternary and quaternary alkaloids in the usual way; the non-quaternary fraction readily yielded *l*-curine (*l*-bebeerine) identical with the alkaloid isolated from natural tube-curare (King, *loc. cit.*). The quaternary fraction crystallised with difficulty but was eventually obtained pure and proved to be, not *d*-tubocurarine chloride as expected, but *l*-tubocurarine chloride.

Folkers and Ugna (*Arch. int. Pharmacodyn.*, 1939, **61**, 373) examined a small specimen of *Ch. tomentosum* collected by Klug and identified by Krukoff, and found evidence of definite curare-like action in the crude quaternary fraction. Wintersteiner and Dutcher (*Science*, 1943, **97**, 467; Dutcher, *J. Amer. Chem. Soc.*, 1946, **68**, 419), however, were able to examine a sample of curare, prepared by Indians of the Upper Amazon, in which only one plant species was used. This was said to have been identified as *Ch. tomentosum* by a botanist at the time of preparation and authenticated by herbarium specimens. From this curare they isolated four non-quaternary bases, one of which was identified as *l*-curine, and a quaternary crystalline alkaloid which proved to be *d*-tubocurarine chloride.

The conclusion to be drawn from these observations, provided the botanical identification of the raw materials has been correct, is that under the name *Ch. tomentosum* there must be two closely allied species which need further differentiation by systematic botanists, one of which yields *l*-curine and *l*-tubocurarine chloride and the other *l*-curine and *d*-tubocurarine chloride. The position is reminiscent of that which held for "pareira brava" until a few years ago (King, *J.*, 1940, 737). Sometimes this drug gave *d*-bebeerine and sometimes *l*-bebeerine, and this was traced to the fact that two closely allied and difficultly distinguishable *Chondrodendron* species were concerned, one of which, *Ch. microphyllum*, gave *d*-bebeerine and the other, *Ch. platyphyllum*, *l*-bebeerine. It is not without interest that *Ch. toxicoferum* (Wedd, Krukoff and Moldenke) (*Ch. polyanthum*, Diels) bears a superficial resemblance to *Ch. tomentosum* and grows like the latter in the Huallaga river valley of the Upper Amazon. Chemical examination of this species is much to be desired.

EXPERIMENTAL.

The stem of *Ch. tomentosum* (667 g.) was powdered and percolated with 1% tartaric acid (10 l.) and the solution then concentrated to 1 l. This solution when neutralised was tested for curare activity on the frog; the paralyzing dose corresponded to 1.0 g. of stem per kg. of frog (compare King, *J.*, 1937, 1478, for definition).

A preliminary assay for alkaloidal content and distribution of activity was carried out on the main solution. Of this, 10 c.c. were treated with chloroform (50 c.c.) and saturated sodium hydrogen carbonate solution (15 c.c.). An amorphous precipitate which formed was removed by filtration, and the aqueous layer was extracted with 3 further portions of chloroform. The chloroform on evaporation

left a syrup which on being moistened with methyl alcohol crystallised, yield 0.5 g. This proved to be *l*-curine, m. p. 213°. The rotation of the dried material was determined in *N*/10-hydrochloric acid; $[\alpha]_{544.1}^{20} = 313^\circ$. Pure *l*-curine under similar conditions gave $[\alpha]_{544.1}^{20} = 340^\circ$ (King, J., 1940, 742). The rotation liquor on evaporation readily crystallised giving *l*-curine hydrochloride, m. p. 282° (efferv.) not depressed by admixture with pure *l*-curine hydrochloride.

The sodium hydrogen carbonate mother liquor and the amorphous precipitate, which had been collected, were separately neutralised with sulphuric acid and assayed by the frog test. It was found that there was approximately twice as much activity in the precipitate (phenolic betaine formation) as in the mother liquor.

On this basis, the main bulk of solution was worked up in a similar way. The total yield of crystalline *l*-curine was 34.1 g. corresponding to a 5% yield on the original stems.

The combined amorphous precipitates produced by bicarbonate and insoluble in chloroform were dissolved in *N*/10-sulphuric acid, concentrated to 1150 c.c., and treated with sulphuric acid (57 g.) followed by 25% phosphotungstic acid in 5% sulphuric acid. The precipitate was converted into the hydrochloride in the usual way, and the solution concentrated to 70 c.c. and treated with saturated aqueous mercuric chloride solution (70 c.c.) followed by addition of solid mercuric chloride (15 g.). The precipitate was decomposed with hydrogen sulphide and the filtered solution evaporated to dryness, yield 5.7 g. (A).

In a similar way the sodium hydrogen carbonate mother liquor was neutralised, concentrated to 800 c.c., precipitated with phosphotungstic acid solution, converted into chloride, and precipitated with mercuric chloride. The mercury-free water soluble residue amounted to 5.6 g. (B).

These two fractions of comparable weights, containing the quaternary alkaloids, were kept as aqueous syrups at 0° for some months; that from the amorphous phenolic-betaines (A) had then crystallised partially. The solid was collected, yield 0.74 g. It was crystallised twice from water and gave *l*-tubocurarine chloride, minute needles, m. p. 275° (efferv.) (Found on hydrated material: loss at 100° (macro), 10.7; (micro), 9.6. OMe (micro), 7.0. $C_{48}H_{44}O_6N_2Cl_2 \cdot 5H_2O$ requires H_2O , 11.5; loss of $4H_2O$, 9.2; 2OMe, 7.9%. Found on dried material (micro): C, 63.5; N, 6.5. $C_{48}H_{44}O_6N_2Cl_2 \cdot H_2O$ requires C, 63.9; H, 6.5%). Partial loss of water of crystallisation on micro-drying had been observed previously for *d*-tubocurarine chloride (King, J., 1935, 1386). The anhydrous salt showed $[\alpha]_{546.1}^{20} = 258^\circ$ (c, 0.38). The rotation of *d*-tubocurarine chloride was determined afresh under comparable conditions and gave $[\alpha]_{546.1}^{20} + 256^\circ$ (c, 0.39) for the anhydrous salt.

The mother liquors of the *l*-tubocurarine chloride were fractionally precipitated with saturated aqueous mercuric chloride and seven fractions collected. Each of these was freed from metallic ions, but no further crystallisation of *l*-tubocurarine chloride could be effected. Each of these fractions was then completely methylated in methyl alcoholic solution with methyl iodide in excess and sodium methoxide, and each gave complex amorphous quaternary iodides. From fraction 6 a crystalline solid was obtained which on further crystallisation from water gave *l*-O-methyltubocurarine iodide clusters of small prisms, m. p. 268° (efferv.), yield 22 mg. (Found: Loss at 95°, 5.5. $C_{40}H_{40}O_6N_2I_2 \cdot 3H_2O$ requires H_2O , 5.6%. Found for the anhydrous salt: C, 51.7; H, 5.6; OMe, 13.8. $C_{40}H_{40}O_6N_2I_2$ requires C, 52.9; H, 5.3; 4OMe, 13.7%). The figure for carbon is low but the same figure was found in duplicate micro-analyses of the dextro-form (King, J., 1935, 1386). *d*-O-Methyltubocurarine iodide had previously been found to melt at 266–267° (efferv.).

It is probable that the *l*-O-methyltubocurarine iodide has arisen from *l*-tubocurarine chloride present in the mother liquors.

The fraction, 5.6 g. (B) above, failed to give *l*-tubocurarine chloride by direct crystallisation. It has not been examined further chemically, but biological assay showed that it contains a more powerful curarising agent than *l*-tubocurarine chloride.

I am indebted to Dr. B. D. Burns of this Institute for a biological assay of *l*-tubocurarine chloride, which, on the isolated rat's diaphragm, was 30 to 60 times weaker than *d*-tubocurarine chloride. The quaternary fraction (B) was about 3.5 times weaker than *d*-tubocurarine chloride, but the active principle contained in it cannot be *d*-tubocurarine chloride.

My thanks are also due to Mr. F. J. Pound, Agronomist to the Department of Agriculture of Trinidad, for help in securing *Ch. tomentosum* whilst in Peru.

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[Received, October 10th, 1946.]

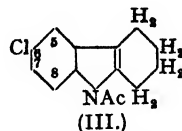
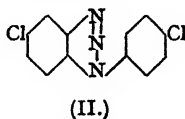
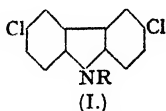
175. *The Friedel-Crafts Reaction in the Carbazole Series. Part III.*

By S. G. P. PLANT and (MRS.) J. F. POWELL.

3:6-Dichloro- and 3:6-dibromo-9-acetylcarbazole were recovered largely unchanged in attempts to apply Friedel-Crafts reactions, but the closely related 6-chloro-9-acetyltetrahydrocarbazole readily gave its 7-acetyl derivative under similar conditions. 6-Bromo-9-acetyl- and 9-acetyl-6-methyl-tetrahydrocarbazole gave analogous products, but several unacetylated tetrahydrocarbazoles proved to be unreactive. 3:6-Dichlorocarbazole, which has been prepared synthetically from 5:4'-dichloro-1-phenylbenzotriazole, gave only *N*-acyl derivatives.

It has been established that under the usual conditions for Friedel-Crafts reactions two acyl groups can be readily introduced into carbazole and its 9-alkyl derivatives in the 3- and the

6-position, but with the 9-acylcarbazoles substitution of a single acyl group in the 2-position ensues (J., 1935, 741; 1936, 1295). It seemed possible that these reactions might be extended to the preparation of substances which would be of value as intermediates for dyes by the use of certain substituted carbazoles, e.g., 3:6-dichloro-9-acetylcarbazole (I; R = Ac). 3:6-Dichlorocarbazole was first prepared by Mazzara and Lamberti-Zanardi (*Gazzetta*, 1896, 26, 236) by heating carbazole with sulphuryl chloride in chloroform, but the constitution of the product appears never to have been rigidly established. This has now been achieved in the form of an unambiguous synthesis by heating 5:4'-dichloro-1-phenylbenzotriazole (II) (the Graebe-Ullmann reaction), which was obtained from 4:4'-dichloro-2-nitrodiphenylamine through the corresponding 2-amino-compound.



3:6-Dichloro-9-acetylcarbazole proved to be unreactive towards acetyl bromide and aluminium chloride in boiling carbon disulphide. Similar lack of reactivity was displayed towards phthalic anhydride and aluminium chloride in nitrobenzene, except that in one experiment, after prolonged standing, a very small quantity of 3:6-dichlorocarbazole-9-phthaloylic acid (I; R = CO·C₆H₄·CO₂H), formed by displacement of the acetyl group, was isolated. 3:6-Dichlorocarbazole itself reacted with phthalic anhydride, benzoyl chloride, and acetyl chloride in the presence of aluminium chloride with the introduction of the corresponding acyl radical, but the substituent was shown in each case to be attached to nitrogen by the fact that it could readily be removed by warming with alkali, and C-acylation was not observed. 3:6-Dibromo-9-acetylcarbazole also failed to react with acetyl bromide under similar conditions.

In contrast, it was found that the closely related 6-chloro-9-acetyltetrahydrocarbazole (III) could be easily converted into 6-chloro-7:9-diacetyltetrahydrocarbazole. This was hydrolysed to 6-chloro-7-acetyltetrahydrocarbazole, the constitution of which was established by reducing it with the Clemmensen reagent. The product, evidently a mixture of 6-chloro-7-ethyltetrahydrocarbazole and 6-chloro-7-ethylhexahydrocarbazole from the fact that it was only partly soluble in dilute acids, was heated with palladised charcoal in an atmosphere of hydrogen with the formation of 2-ethylcarbazole. The result is in harmony with the observations of Plant and Rogers (J., 1936, 40) who found that the 7-acetyl and 7-benzoyl derivatives were obtained when 9-acetyl- and 9-benzoyl-tetrahydrocarbazole were submitted to Friedel-Crafts reactions with acetyl bromide and benzoyl chloride. It was not, however, possible to obtain an analogous phthaloylic acid from 6-chloro-9-acetyltetrahydrocarbazole by the use of phthalic anhydride.

An acetyl group has been similarly introduced into 6-bromo-9-acetyltetrahydrocarbazole and 9-acetyl-6-methyltetrahydrocarbazole, the products being evidently 6-bromo-7:9-diacetyl- and 7:9-diacetyl-6-methyl-tetrahydrocarbazole respectively. The latter was hydrolysed to 7-acetyl-6-methyltetrahydrocarbazole.

A surprising observation is that unacetylated tetrahydrocarbazole, and its 6-chloro-, 6-bromo-, 6-methyl-, and 6-acetamido-derivatives, were recovered unchanged after treatment with acetyl bromide and aluminium chloride in carbon disulphide, even with prolonged boiling. This is remarkable in view of the ease with which carbazole undergoes substitution.

EXPERIMENTAL.

Synthesis of 3:6-Dichlorocarbazole.—After a mixture of 2:5-dichloronitrobenzene (16 g.), p-chloroaniline (12 g.), and potassium carbonate (12 g.) had been heated at 220° for an hour, unchanged materials were removed in steam and the residue crystallised from alcohol, 4:4'-dichloro-2-nitrodiphenylamine being obtained in crimson needles, m. p. 149–150° (cf. Blom, *Helv. Chim. Acta*, 1921, 4, 1038). The nitro-compound (1·2 g.) in hot glacial acetic acid (20 c.c.) was treated gradually with stannous chloride (6 g.) dissolved in hydrochloric acid (20 c.c. of 28%), and the solution boiled for 10 minutes, cooled, and made alkaline with concentrated aqueous potassium hydroxide. The precipitated amine separated from alcohol in colourless needles, m. p. 137°. Its suspension in glacial acetic acid was treated with aqueous sodium nitrite, and, after the addition of water, the precipitated 5:4'-dichloro-1-phenylbenzotriazole was crystallised from alcohol and obtained in brown needles, m. p. 175° (Found: N, 15·9. C₁₂H₈N₂Cl₂ requires N, 15·9%). When this substance was heated for an hour at 360° and the product distilled under reduced pressure, 3:6-dichlorocarbazole, colourless prisms, m. p. 202°, from glacial acetic acid, was obtained. It proved to be identical (mixed m. p.) with the material obtained by the chlorination of carbazole as described by Mazzara and Lamberti-Zanardi (*loc. cit.*).

Attempted Friedel-Crafts Reactions with 3:6-Dichlorocarbazole.—(a) A solution of 3:6-dichlorocarbazole (2 g.), phthalic anhydride (2 g.), and aluminium chloride (2 g.) in nitrobenzene (25 c.c.) was left

at room temperature for 4 days and then treated with ice-dilute hydrochloric acid, and the solvent removed in steam. After the residue had been dissolved in hot alcohol and poured into dilute ammonia, the filtered aqueous solution was acidified, and 3 : 6-dichlorocarbazole-9-phthaloylic acid, colourless needles, m. p. 185° (rapid heating), from glacial acetic acid, obtained (Found: Cl, 18.2. $C_{20}H_{11}O_3NCl_2$ requires Cl, 18.5%). When its solution in aqueous ammonia was boiled, a precipitate of 3 : 6-dichlorocarbazole, identified by mixed m. p., soon appeared. Similar results were obtained when the reaction was carried out in nitrobenzene at 60° for 6 hours.

(b) Benzoyl chloride (2.5 g.) was added to 3 : 6-dichlorocarbazole (2 g.) and aluminium chloride (2.5 g.) in carbon disulphide (25 c.c.), and the whole refluxed for an hour. After the carbon disulphide had been distilled off, the residue poured into ice-dilute hydrochloric acid, and the excess of benzoyl chloride removed in steam, 3 : 6-dichloro-9-benzoylcarbazole remained; it separated from glacial acetic acid in almost colourless needles, m. p. 204° (Found: Cl, 20.3. $C_{19}H_{11}ONCl_2$ requires Cl, 20.9%). When its solution in aqueous-alcoholic potassium hydroxide was boiled for 1½ hours and poured into water, 3 : 6-dichlorocarbazole was precipitated.

(c) After 3 : 6-dichlorocarbazole had been treated with acetyl chloride and aluminium chloride under conditions similar to those used with benzoyl chloride, 3 : 6-dichloro-9-acetylcarbazole, colourless prisms, m. p. 185°, from glacial acetic acid, was obtained. It was identical (mixed m. p.) with the substance obtained by boiling 3 : 6-dichlorocarbazole with acetic anhydride and a drop of concentrated sulphuric acid under reflux (cf. Mazzara and Lamberti-Zanardi, *loc. cit.*).

6-Chloro-7-acetyltetrahydrocarbazole.—Aluminium chloride (2 g.) was added to a mixture of 6-chloro-9-acetyltetrahydrocarbazole (2 g., prepared as described by Plant and Rosser, *J.*, 1928, 2454) and acetyl bromide (1.5 c.c.) in carbon disulphide (30 c.c.), and the whole refluxed for 10 minutes. After the solvent had been distilled off, the residue added to ice-dilute hydrochloric acid, and the solid crystallised from alcohol, 6-chloro-7 : 9-diacetyltetrahydrocarbazole was obtained in colourless needles, m. p. 118° (Found: C, 66.5; H, 5.2. $C_{16}H_{14}O_2NCl$ requires C, 66.3; H, 5.5%). The reaction proceeded less readily when acetyl chloride was used. When a solution of the diacetyl compound (1 g.) in alcohol (10 c.c.) containing potassium hydroxide (0.6 g.) and water (0.5 c.c.) was refluxed for an hour, filtered, and allowed to cool, 6-chloro-7-acetyltetrahydrocarbazole separated. It was recrystallised from alcohol and isolated in almost colourless prisms, m. p. 171° (Found: C, 68.1; H, 6.0; N, 5.9. $C_{16}H_{14}ONCl$ requires C, 67.9; H, 5.7; N, 5.7%).

Acetyl chloride (0.7 c.c. in a little acetone) was gradually added with constant shaking to the 7-acetyl compound (0.5 g.) dissolved in acetone (10 c.c.) containing aqueous potassium hydroxide (0.45 g. of 66%). Water then precipitated 6-chloro-7 : 9-diacetyltetrahydrocarbazole, which was crystallised from alcohol and found to be identical (mixed m. p.) with the substance described above.

Conversion of 6-Chloro-7-acetyltetrahydrocarbazole into 2-Ethylcarbazole.—6-Chloro-7-acetyltetrahydrocarbazole (2.6 g.) and concentrated hydrochloric acid (50 c.c.) were shaken with amalgamated granulated zinc (200 g.), and the whole was left overnight. After the addition of anisole (5 c.c.) and more concentrated hydrochloric acid (30 c.c.), the mixture was refluxed for 12 hours, the product extracted with ether, the extract evaporated, and anisole removed from the residue by distillation in steam. The less volatile material, which was only partly soluble in dilute acids, was again extracted with ether, and the extract dried (K_2CO_3) and evaporated. When the residue was mixed with 25% of its weight of palladised charcoal and heated at 300–320° for 11 hours in an atmosphere of hydrogen, hydrogen chloride was freely evolved in the early stages. The product was dissolved in warm acetone and recovered from the filtered solution by the addition of water. After it had been distilled under reduced pressure and crystallised from glacial acetic acid, 2-ethylcarbazole was obtained in colourless plates, m. p. 218–220°, identical (mixed m. p.) with the substance prepared by Plant and Williams (*J.*, 1934, 1142).

6-Bromo-7 : 9-diacetyltetrahydrocarbazole.—After a solution of 6-bromotetrahydrocarbazole (25 g., Borsche, Witte, and Bothe, *Annalen*, 1908, 359, 53) in acetic anhydride (90 c.c.) containing a few drops of concentrated sulphuric acid had been refluxed for 6 hours, 6-bromo-9-acetyltetrahydrocarbazole separated on cooling. It was recrystallised from alcohol (charcoal) and obtained in colourless plates (15 g.), m. p. 120° (Found: N, 4.7. $C_{16}H_{14}ONBr$ requires N, 4.8%). Aluminium chloride (4 g.) was added to a mixture of this acetyl compound (2 g.) and acetyl chloride (6 c.c.) in carbon disulphide (25 c.c.), and the whole refluxed for 15 minutes and treated as described for the corresponding chloro-compound. When the product was crystallised from alcohol, 6-bromo-7 : 9-diacetyltetrahydrocarbazole separated in colourless needles, m. p. 112° (Found: N, 4.2. $C_{16}H_{14}O_2NBr$ requires N, 4.2%). The use of acetyl bromide gave less satisfactory products.

When the diacetyl compound (3 g.) in hot glacial acetic acid (10 c.c.) was treated with concentrated nitric acid (1.2 g.), oxides of nitrogen were evolved, and 6-bromo-10 : 11-dihydroxy-7 : 9-diacetylhexahydrocarbazole separated on cooling. On crystallisation from alcohol, it was obtained in colourless plates, m. p. 210° (decomp.) (Found: C, 52.0; H, 4.9. $C_{16}H_{18}O_4NBr$ requires C, 52.2; H, 4.9%).

7-Acetyl-6-methyltetrahydrocarbazole.—When treated with acetyl bromide and aluminium chloride as described for the corresponding chloro-compound, 9-acetyl-6-methyltetrahydrocarbazole (Manjunath and Plant, *J.*, 1926, 2260) gave 7 : 9-diacetyl-6-methyltetrahydrocarbazole, colourless needles, m. p. 136°, from alcohol (Found: C, 75.6; H, 7.1. $C_{17}H_{16}O_2N$ requires C, 75.8; H, 7.1%). Hydrolysis as for the chloro-compound led to 7-acetyl-6-methyltetrahydrocarbazole, colourless plates, m. p. 207°, from alcohol (Found: C, 78.7; H, 7.4. $C_{18}H_{17}ON$ requires C, 79.3; H, 7.5%).

The authors are indebted to Imperial Chemical Industries Limited for grants.

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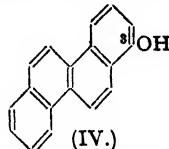
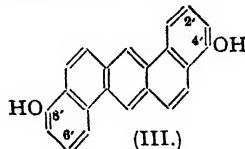
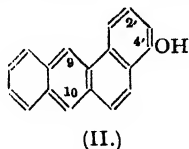
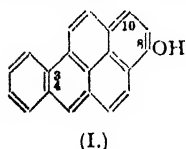
[Received, October 12th, 1946.]

176. Polycyclic Aromatic Hydrocarbons. Part XXXII. 2'-Methoxy- and 2'-Methoxy-9 : 10-dimethyl-1 : 2-benzanthracene.

By G. M. BADGER.

2'-Methoxy-1 : 2-benzanthracene and 2'-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene have been prepared by the scheme illustrated in formulæ (V—XII), for comparison with the (methylated) metabolic products of 1 : 2-benzanthracene and of 9 : 10-dimethyl-1 : 2-benzanthracene, in rabbits.

IN mice and rats, carcinogenic and related polycyclic hydrocarbons are metabolised to phenolic derivatives (I—IV) in which the hydroxy-group occupies the same relative position (Berenblum and Schoental, *Biochem. J.*, 1945, Proc. lxiv). In rabbits, however, 1 : 2 : 5 : 6-dibenzanthracene



is metabolised to a dihydroxy-derivative which differs from that obtained from mice and rats. This compound has not yet been identified, although several of the 55 possible isomers have been excluded (for references see Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681; 1941, **63**, 1256). The synthesis of all the remaining isomers would be a difficult task, and the present work was undertaken to provide a clue to the identity of the rabbit metabolite of dibenzanthracene. For this purpose, it was decided to prepare hydroxy-derivatives of 1 : 2-benzanthracene, which could then be compared with the metabolic products of this hydrocarbon, in rabbits. By analogy with dibenzanthracene, it is probable that the rabbit will metabolise benzanthracene to a hydroxy-derivative other than, or in addition to, the 4'-hydroxy-derivative.

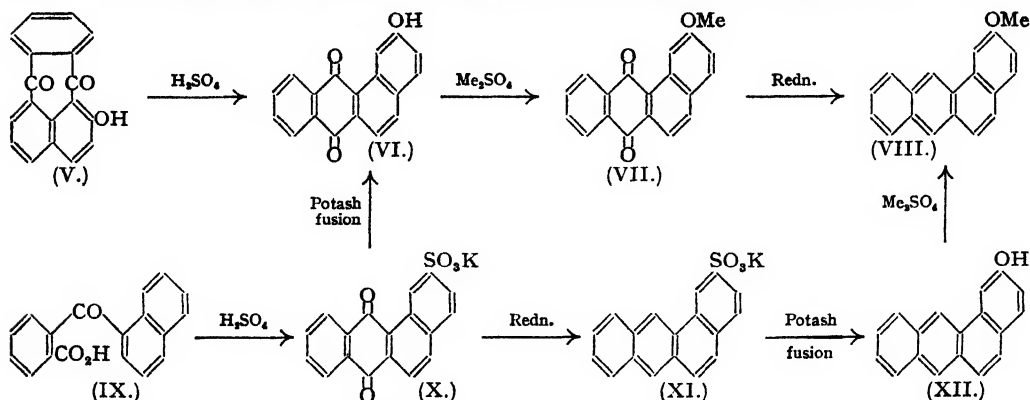
Since rats oxidise benzanthracene and dibenzanthracene at positions which are liable to chemical attack when the *meso*-positions are blocked (Cason and Fieser, *loc. cit.*), it appeared probable that the rabbit would oxidise the same compounds at some other positions which are also liable to chemical attack. In benzantraquinone, this is the 2'-position, for Joffe and Fedorova (*J. Gen. Chem. Russia*, 1941, **11**, 619) have shown that, at high temperatures, benzantraquinone is sulphonated at this position. (Other positions of the benzantraquinone and benzanthracene molecules may also be subject to substitution reactions under certain conditions; see Scholl, *Ber.*, 1911, **44**, 2370; Cook and Hewett, *J.*, 1933, 1408.)

The fact that Berenblum and Schoental (*Cancer Res.*, 1946, **6**, 699) have confirmed the presence of 10-hydroxy-3 : 4-benzpyrene as well as 8-hydroxy-3 : 4-benzpyrene (I) in the excreta of both rats and rabbits, and that more of the 10-hydroxy-derivative is formed in the rabbit, lends added support to this view. For these reasons 2'-methoxy-1 : 2-benzanthracene and 2'-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene have been prepared. The comparison of the former with the (methylated) rabbit metabolic products has been undertaken by Drs. Berenblum and Schoental. Such of the compounds as appear to be suitable will be tested for biological action by Professor A. Haddow. Results of these investigations will be published elsewhere.

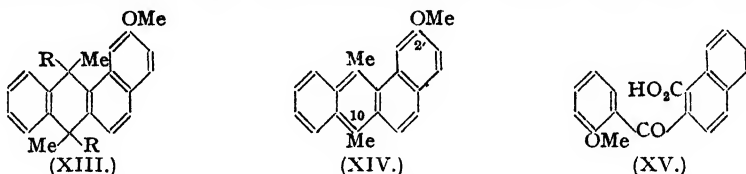
2'-Hydroxy-1 : 2-benzanthracene (XII) was prepared by sulphonation of 2-(1'-naphthoyl)-benzoic acid (IX), followed by reduction and potash fusion, a method substantially the same as that reported by Joffe and Fedorova (*loc. cit.*) except that naphthoylbenzoic acid was used instead of benzantraquinone. Since the melting point of the final product (XII) did not agree with that reported by the Russian workers (although the melting points of the acetates were substantially in agreement), the scheme outlined in formulæ (V—XII) was carried out.

Phthaloylnaphthol (V) was converted into 2'-hydroxy-1 : 2-benzanthraquinone (VI) by the method of Fieser and Fieser (*J. Amer. Chem. Soc.*, 1933, **55**, 3342). The 50% yield claimed by these authors could not, however, be confirmed. In 35—40 runs, the yield of pure product averaged about 10%. The same compound was also prepared by fusion of potassium 1 : 2-benzanthraquinone-2'-sulphonate (X) with potassium hydroxide by the method of Joffe and Fedorova. Methylation with methyl sulphate gave 2'-methoxy-1 : 2-benzanthraquinone (VII), which was reduced with stannous chloride, followed by zinc and alkali, to 2'-methoxy-1 : 2-benzanthracene (VIII). The same compound was also prepared by methylation of 2'-hydroxy-1 : 2-benzanthracene obtained following the sulphonation of naphthoylbenzoic acid (IX—XII).

Treatment of 2'-methoxy-1:2-benzanthraquinone (VII) with methylmagnesium iodide gave 9:10-dihydroxy-2'-methoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene (XIII, R = OH).



R = OH). Methylation with methyl alcohol and a trace of sulphuric acid gave 2':9:10-tri-methoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene (XIII, R = OMe), which, on treatment with sodium, gave 2'-methoxy-9:10-dimethyl-1:2-benzanthracene (XIV) (cf. Bachmann and Chmerda, *J. Org. Chem.*, 1939, 4, 583; *J. Amer. Chem. Soc.*, 1938, 60, 1023).



The Friedel-Crafts reaction between phthalic anhydride and β -methoxynaphthalene, in tetrachloroethane solution, is known to give 2-(2'-hydroxynaphthoyl-1')-benzoic acid or its methyl ether (Fieser, *J. Amer. Chem. Soc.*, 1931, 53, 3546). When nitrobenzene is used as a solvent, the course of Friedel-Crafts reactions between β -methoxynaphthalene and various compounds, especially acyl chlorides, is modified, so that substitution occurs not at the 1-position but at the 6-position (for references, see Hudson, *J.*, 1946, 76). This does not appear to take place with aryl groups, for Hudson (*loc. cit.*) found that the anisoyl group enters the 1-position. The present work shows that phthalic anhydride also reacts at the 1-position, even in cold nitrobenzene solution. In an attempt to convert 2-(2'-hydroxynaphthoyl-1')-benzoic acid lactone into 2'-hydroxy-1:2-benzanthraquinone with sulphuric acid, only phthaloylnaphthol (V) and phthalic acid were formed. That the CO bond at the 1-position should be broken under these conditions is of special interest in view of the conversion of phthaloylnaphthol into 1:2-benzanthraquinone.

In an attempt to prepare 5-hydroxy-1:2-benzanthracene, the Grignard solution from *o*-bromoanisole was condensed with 1:2-naphthalic anhydride. Attempts to prepare the benzanthraquinone from the resulting 2-(2'-methoxybenzoyl)-1-naphthoic acid (XV), by treatment either with sulphuric acid or with benzoyl chloride and a trace of sulphuric acid (Badger and Cook, *J.*, 1939, 802), were unsuccessful.

EXPERIMENTAL.

2'-Hydroxy-1:2-benzanthraquinone.—(i) This was prepared essentially as described by Fieser and Fieser (*loc. cit.*), but the yield claimed could not be confirmed. Phthaloylnaphthol (10 g.) was added to a solution of water (25 c.c.) and sulphuric acid (50 c.c.) and the mixture brought to the boil, with stirring. When oil separated, the mixture was poured on ice (200 g.). The product was extracted with a little boiling alcohol, and some unchanged phthaloylnaphthol filtered off. The crude 2'-hydroxy-1:2-benzanthraquinone obtained from the alcohol was dried, and refluxed for 1 hour with acetic anhydride and sodium acetate. The yellow needles which separated on cooling (1.6 g.) gave, on recrystallisation from acetic acid, 2'-acetoxy-1:2-benzanthraquinone, m. p. 254–255° (1 g.). The acetic acid liquors yielded colourless plates (0.4 g.) which after purification had m. p. 213–214°. This was evidently acetoxyphthaloylnaphthalene (Found: C, 76.1; H, 3.7. Calc. for $\text{C}_{20}\text{H}_{12}\text{O}_4$: C, 76.0; H, 3.8%). Pure 2'-hydroxy-1:2-benzanthraquinone, m. p. 253–253.5°, was obtained from the acetate by hydrolysis with alcoholic sodium hydroxide followed by recrystallisation from alcohol.

(ii) A mixture of 2-(1'-naphthoyl)benzoic acid (15 g.) and concentrated sulphuric acid (150 c.c.) was heated on the water-bath for 1 hour, and then at 160–160° for 6 hours. The dark red solution was poured on ice (150 g.), and the sulphonic acid collected and sucked as dry as possible with the water-pump. The paste was dissolved in hot water, and the solution made alkaline with barium hydroxide. Potassium sulphate (5.1 g.) was added, and the mixture heated on the steam-bath for 2 hours. The filtrate, on evaporation to dryness, gave crude potassium 1:2-benzanthraquinone-2'-sulphonate (13.5 g.). After fusion with potassium hydroxide as described by Joffe and Fedorova (*loc. cit.*) this gave 2'-hydroxy-1:2-benzanthraquinone, identical with that prepared by the first method.

2'-Methoxy-1:2-benzanthraquinone.—2'-Hydroxy-1:2-benzanthraquinone (1.9 g.) was methylated in the usual way by the alternate addition of methyl sulphate and sodium hydroxide, at the temperature of the steam-bath, until a portion of the alkaline filtrate gave no precipitate with hydrochloric acid. Recrystallised from acetic acid, the 2'-methoxy-1:2-benzanthraquinone (1.83 g.) formed long golden-brown needles, m. p. 200–201° (Found: C, 79.3; H, 4.3. $C_{22}H_{14}O_2$ requires C, 79.2; H, 4.2%).

2':9:10-Trimethoxy-1:2-benzanthracene.—2'-Hydroxy-1:2-benzanthraquinone (0.4 g.) was methylated with methyl sulphate and potassium hydroxide in the presence of zinc dust (2 g.) at 100°. The residue after filtration was extracted with boiling alcohol, and the alcohol decolourised with charcoal and concentrated. The 2':9:10-trimethoxy-1:2-benzanthracene (0.21 g.) formed almost colourless crystals, m. p. 173.5–175° (Found: C, 79.4; H, 5.4. $C_{24}H_{18}O_3$ requires C, 79.3; H, 5.7%).

2'-Methoxy-1:2-benzanthracene.—(i) 2'-Methoxy-1:2-benzanthraquinone (0.25 g.), stannous chloride (1.5 g.), hydrochloric acid (3 c.c.) and acetic acid (5 c.c.) were boiled under reflux for 1 hour. The solution was poured into water, and after 1 hour the solid was transferred to a flask containing 2N-sodium hydroxide (15 c.c.) and zinc dust (1 g.). The mixture was boiled under reflux for 3½ hours, cooled, and filtered. The residue was extracted several times with boiling alcohol, and the solution concentrated and allowed to crystallise. The 2'-methoxy-1:2-benzanthracene (0.1 g.) formed almost colourless flat needles, m. p. 165–166° (Found: C, 88.4; H, 5.3. $C_{18}H_{14}O$ requires C, 88.4; H, 5.4%). The alcoholic solution showed an intense blue fluorescence in daylight.

The *picrate*, prepared in alcohol, formed red-brown needles, m. p. 170–171° (Found: C, 61.9; H, 3.6; N, 8.7. $C_{22}H_{14}O_5N_3$ requires C, 61.6; H, 3.5; N, 8.6%).

(ii) Potassium 1:2-benzanthraquinone-2'-sulphonate (7.5 g.) was reduced by 12 hours' boiling with zinc dust (14 g.) in water (300 c.c.) and ammonia (d 0.880; 75 c.c.). The resulting potassium 1:2-benzanthracene-2'-sulphonate (2.6 g.) was obtained as colourless plates from water. This salt (1.6 g.) was converted into the phenol by fusion at 290–300°, for 1 hour, with potassium hydroxide (8 g.). The 2'-hydroxy-1:2-benzanthracene (0.7 g.) formed pale yellow plates from acetic acid, m. p. 191.5–193.5° (lit. 178–179°) (Found: C, 88.5; H, 4.7. Calc. for $C_{18}H_{14}O$: C, 88.5; H, 4.9%). The acetate, prepared by refluxing a portion with acetic anhydride and sodium acetate, formed colourless silky needles, m. p. 156.5–158.5° (lit. 152–153°) (Found: C, 84.1; H, 4.8. Calc. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9%). The above hydroxybenzanthracene was methylated in almost quantitative yield by the alternate addition of methyl sulphate and sodium hydroxide. The product, crystallised from alcohol, was identical with the 2'-methoxy-1:2-benzanthracene prepared by the first method.

2':9:10-Trimethoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene.—2'-Methoxy-1:2-benzanthraquinone (2 g.), suspended in a Soxhlet thimble under the condenser (compare Bachmann and Chmerda, *J. Org. Chem.*, 1939, 4, 583), dissolved after the Grignard solution (from methyl iodide (3 c.c.), ether (15 c.c.), and benzene (40 c.c.)) had been refluxed for 5 hours. After decomposition with ice-cold ammonium chloride, the organic layer was dried and evaporated. The gummy residue crystallised on stirring with benzene-light petroleum. 2'-Methoxy-9:10-dihydroxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene (1.2 g.) formed colourless micro-crystals, from benzene, m. p. 157–160° (decomp.) (Found: C, 78.9; H, 6.3. $C_{24}H_{20}O_2$ requires C, 78.8; H, 6.3%). The methyl ether was obtained by dissolving the diol in methyl alcohol and treating the cold solution with sulphuric acid (2 drops) in methyl alcohol (5 c.c.). It formed colourless needles, from methyl alcohol, m. p. 171–172° (Found: C, 79.4; H, 6.9. $C_{26}H_{22}O_2$ requires C, 79.3; H, 6.9%).

2'-Methoxy-9:10-dimethyl-1:2-benzanthracene.—This was prepared by treatment of the above methyl ether with sodium (cf. Bachmann and Chmerda, *loc. cit.*). Recrystallised from methyl alcohol, 2'-methoxy-9:10-dimethyl-1:2-benzanthracene formed pale yellow lustrous plates, m. p. 112–113° (Found: C, 88.0; H, 6.3. $C_{24}H_{20}O$ requires C, 88.1; H, 6.3%). Its alcoholic solution showed an intense blue fluorescence in daylight.

In one experiment a colourless compound, presumably the *photo-oxide*, was also isolated (cf. Sandin and Fieser, *J. Amer. Chem. Soc.*, 1940, 62, 3098). It formed colourless needles from alcohol, m. p. 210–212° (after sintering) (Found: C, 79.25; H, 5.45. $C_{22}H_{14}O_3$ requires C, 79.3; H, 5.7%).

2-(2'-Methoxynaphthoyl-1')-benzoic acid.—β-Methoxynaphthalene (7.5 g.), phthalic anhydride (8.0 g.), and nitrobenzene (100 c.c.) were cooled in ice and treated with aluminium chloride (12.5 g.) during 1 hour, with stirring. After 3 hours, the solution was kept at room temperature, with shaking, for 70 hours. After decomposition in the usual way, the acid was obtained; it crystallised from toluene as yellow prisms (4.5 g.), m. p. 191–194°. Its constitution was proved by demethylation with aluminium chloride in boiling benzene, followed by conversion into the lactone, m. p. 195–196° (Fieser, *J. Amer. Chem. Soc.*, 1931, 53, 3546).

The same hydroxy-acid was obtained, in poor yield, following a similar experiment with β-naphthol.

Action of Sulphuric Acid on 2-(2'-Hydroxynaphthoyl-1')-benzoic Acid Lactone.—A solution of the lactone (1 g.) in concentrated sulphuric acid (10 c.c.) was heated at 60–70° for 6 hours, and then poured on ice. The solid obtained was dissolved in aqueous alcohol, from which phthaloylnaphthol, m. p. 196–197° (alone, or mixed with an authentic specimen) (0.08 g.), was obtained. The alcoholic liquors, on evaporation, deposited phthalic acid (0.26 g.), m. p. 196° (Found: C, 57.6; H, 3.7. Calc. for $C_8H_6O_4$: C, 57.8; H, 3.6%), converted into phthalic anhydride, m. p. 128–130°, by sublimation. Phthalic acid was also obtained following a similar experiment with the free acid. Both the free acid and the lactone gave cherry-red solutions in sulphuric acid.

2-(2'-Methoxybenzoyl)-1-naphthoic Acid.—A solution in ether (30 c.c.) and benzene (15 c.c.) of

o-anisylmagnesium bromide (from 25 g. of *o*-bromoanisole) was added slowly to a boiling solution of 1 : 2-naphthalic anhydride (26.4 g.) in anhydrous benzene (200 c.c.). The thick yellow precipitate was filtered off and decomposed with ice and dilute sulphuric acid in the presence of ether. The ether solution was extracted with sodium carbonate, and the acid precipitated (20 g.). After purification through the acetoxy-lactone, it formed colourless transparent prisms, m. p. 185–187° (Found: C, 74.45; H, 4.6. $C_{19}H_{14}O_4$ requires C, 74.45; H, 4.6%). The acetoxy-lactone, prepared by heating the acid (20 g.) with acetic anhydride (40 c.c.) and pyridine (130 c.c.) on the steam-bath for 2 hours, formed colourless transparent prisms, from toluene, m. p. 209–211° (Found: C, 72.9; H, 4.7. $C_{21}H_{16}O_5$ requires C, 72.4; H, 4.6%). Attempts to ring-close the acid with sulphuric acid, or with benzoyl chloride and a trace of sulphuric acid, were unsuccessful.

The author thanks Professor J. W. Cook, F.R.S., for his interest in this work, which has been made possible by the award of an Imperial Chemical Industries Research Fellowship. All analyses are microanalyses by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW.

[Received, October 7th, 1946.]

177. *New Potential Chemotherapeutic Agents. Part VII.* *Experiments on the Synthesis of 8-Aminopurines.*

By F. E. KING and T. J. KING.

With the possibility that the synthesis of potential adenine inhibitors might lead to a plasmodicidal compound, the preparation of basically-substituted purines related to adenine, e.g. (II; $R = NH \cdot [CH_2]_3 \cdot NEt_3$), has been investigated. The principal intermediates obtained in this research are the previously unknown purines (V; $R = NHPh$) and (VI; $R = OH$), and the triazole (IX; $R = Me$), but only in (VI; $R = OH$), the methylthio-group of which does not react with amines, was it possible to replace the 6-hydroxyl group by a basic substituent. The arylcarbamides (IV; $R = SH$) and (IV; $R = NH_2$) were resistant to cyclisation, but the derivative (IV; $R = OH$) was successfully converted into (V; $R = NHPh$), which was also directly obtained from the hydrochloride of (III) and phenylcyanamide in boiling butanol, possibly through the *O*-butyl ether (IV; $R = O \cdot C_4H_9$).

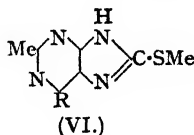
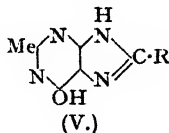
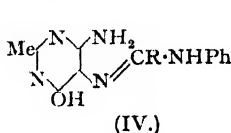
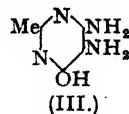
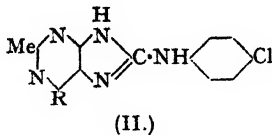
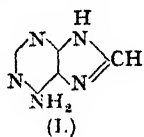
In its application to antimalarial compounds, the current theory as to the mode of action of the more specific chemotherapeutic agents was first expressed by Oesterlin (*Klin. Woch.*, 1936, 15, 1719), who suggested that the activity of mepacrine and pamaquin arose from their easy reduction to dihydro-derivatives, a property which enabled them to inhibit some riboflavin-containing enzyme essential to the metabolism of the parasite. The close structural resemblance of these drugs to riboflavin is in agreement with this idea, and the ability, not only of mepacrine but also of some of the newer pyrimidine antimalarials (see Curd and Rose, *J.*, 1946, 343 *et seq.*), to function as riboflavin antagonists has recently been experimentally demonstrated in nutritional investigations with *Lactobacillus casei* by Madinaveitia (*Biochem. J.*, 1946, 40, 373).

If, as these observations seem to imply, antimalarial action is dependent on the inhibition of well-known enzymes, it should also be possible, by means of suitably constituted reagents, to arrest the growth of the plasmodia by interfering with the synthesis or utilisation of other co-enzyme constituents, for example, the purines adenine and guanine. Such a hypothesis has, in fact, lately been propounded by Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 360) to account for the antimalarial properties of certain 5-methylpyrimidines, which these authors consider may be due to blocking of the purine biosynthesis by the 5-substituent. From considerations similar to those advanced by Todd and his colleagues (*loc. cit.*), it occurred to us that useful results might follow from the preparation of purine bases as potential antimalarial agents, and we were for a time engaged in the synthesis of appropriately substituted compounds related to adenine (I).

The derivatives of (I) considered most likely to possess biological activity were those incorporating the characteristic dialkylaminoalkylamino- side chain and the chlorinated or methoxylated aniline residue typical of what may be termed the riboflavin antimalarials. Of the several possible arrangements of these presumably essential components about the adenine, or somewhat more readily obtainable 2-methyladenine, nucleus, that shown as (II; $R = NH \cdot [CH_2]_3 \cdot NEt_3$) was selected as the first objective. Although the project has made some progress, its full development has been hindered by unexpected difficulties, the nature of which is indicated in the following account of the experiments.

With 4 : 5-diamino-6-hydroxy-2-methylpyrimidine (III) as the starting point, the sequence of reactions in the proposed synthesis of (II; $R = NH \cdot [CH_2]_3 \cdot NEt_3$) was (i) formation of the 5-*p*-chlorophenylthiocarbamido-derivative; (ii) its cyclisation to 8-*p*-chloroanilino-6-hydroxy-2-methylpurine (II; $R = OH$); (iii) replacement of the 6-hydroxyl group by chlorine, giving

(II; R = Cl); and (iv) substitution of the chlorine by a diethylaminopropylamino-group. Since there was no reason to suppose that the necessary conditions would be appreciably affected by slight variations in structure, the reactions were for the most part investigated with the anilino- rather than the *p*-chloroanilino-derivatives.



The action of ammonium phenyldithiocarbamate on the diaminopyrimidine (III) in aqueous solution at 100° gave the 5-phenylthiocarbamido-derivative (IV; R = SH), but the latter remained unchanged on attempted ring-closure in boiling water, and with lead hydroxide in refluxing ethanol or isoamyl alcohol. Methylation to the potentially more reactive methylthio-compound (IV; R = SMe) could not be accomplished. However, prolonged heating of (IV; R = SH) with pyridine effected cyclisation, but with the elimination of aniline, so that the product was 6-hydroxy-8-mercapto-2-methylpurine (V; R = SH). The constitution of this compound was confirmed by means of an independent synthesis from the diamine (III) by fusion with thiourea, and also by the formation of 6-hydroxy-8-methylthio-2-methylpurine (V; R = SMe) on treatment with methyl iodide in aqueous sodium hydroxide. Unfortunately, the methylthio-derivative could not be utilised for the synthesis of the 8-anilino-purine (V; R = NHPh), or even of (V; R = NH·[CH₂]₃·NET₂), since it failed to react with either aniline or γ -diethylaminopropylamine.

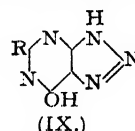
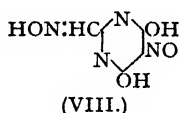
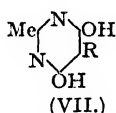
In order to permit of the use of other methods of ring-closure to the required base (V; R = NHPh), the original scheme was modified by substituting as an intermediate 4-amino-5-(N'-phenylcarbamido)-6-hydroxy-2-methylpyrimidine (IV; R = OH), which was prepared from (III) by the action of phenyl isocyanate in boiling toluene. Treatment of the carbamidopyrimidine with both phosphoryl chloride and phosphorus pentachloride under various conditions did not succeed in giving any purifiable substance, but with phosphorus trichloride in refluxing toluene a product having the composition of the required 8-anilino-6-hydroxy-2-methylpurine (V; R = NHPh) was obtained. Since there is also a possibility of reaction between the substituents at the 5- and the 6-position, which would result in the formation of 6-amino-8-hydroxy-9-phenyl-2-methylpurine, the synthesis did not provide definite proof of the constitution of the new base. Moreover, the product exhibited an unexpected stability towards chlorinating agents, a property which could be interpreted as a further manifestation of the inertness of the 8-substituent already encountered in the analogous 8-methylthiopurine (V; R = SMe). Accordingly, a method was designed for the synthesis of (V; R = NHPh) which would leave the structure of the final product in no doubt. This involved the preparation of the guanidine (IV; R = NH₂) which was effected by prolonged heating of (III), in the form of its hydrochloride, with phenylcyanamide in refluxing ethanol. The condensation was repeated with *p*-chlorophenylcyanamide, both guanidines being further identified by their hydrochlorides and picrates, but in no circumstances could the cyclisation of either guanidine be achieved. Nevertheless, the product (V; R = NHPh) was ultimately obtained when attempting to accelerate the reaction of phenylcyanamide with the pyrimidine (III) by using boiling butanol instead of ethanol as solvent. The base gave a dihydrated hydrochloride and was in every respect identical with the substance already prepared from (IV; R = OH), the constitution of which is thus established.

The derivative (IV; R = NH₂) could not be detected in the reaction product, and together with the fact that it failed to cyclise under similar conditions, it is fairly certain that the guanidine is not an intermediate in the cyclisation. It is possible to suggest an explanation for the variation of product with solvent if the likely supposition is made that a preliminary step is the formation from the cyanamide of an imino-ether, Ph·NH·C(=NH)·O-alkyl. Two alternatives are then possible in the subsequent condensation with the pyrimidine 5-amino-group: (i) elimination of alcohol, giving the guanidine (IV; R = NH₂); or (ii) loss of ammonia, a reaction

similar to that introduced by Schmidt (*Ber.*, 1914, 47, 2548) for the preparation of *N*-substituted imino-ethers, giving (IV; R = O-alkyl). Normally, guanidine formation would be expected to occur, but when O-alkyl is the comparatively inert butoxy-group, formation of the substituted imino-ether (IV; R = O·C₄H₉) would take precedence, the final ring-closure to (V; R = NHPh), a reaction of the amidine type, being facilitated by the favourable spatial configuration of the molecule.

Since the anilino-hydroxypurine (V; R = NHPh) was highly resistant to attack by chlorinating agents, further progress in the direction of (II; R = dialkylaminoalkylamino-) was impossible. Shortly afterwards, Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, 67, 1271) reported similar difficulties in attempting to convert guanine hydrochloride into 6-chloro-2-aminopurine. These results are surprising, particularly when compared with those from later experiments on the methylthiopurine (V; R = SMe). Under the conditions used by Baddiley and Topham (*J.*, 1944, 678) for the preparation of trichloropyrimidine from barbituric acid, *viz.*, heating with phosphoryl chloride and dimethylaniline, the only isolable product was a small yield of 6-*N*-methylanilino-8-methylthio-2-methylpurine (V; R = NMePh), but, with phosphoryl chloride alone, no difficulty was experienced in obtaining the 6-chloro-8-methylthio-2-methylpurine (VI; R = Cl). Heating the latter in toluene with γ -diethylaminopropylamine gave the corresponding basically-substituted purine (VI; R = NH·[CH₂]₃·NEt₂) which was isolated as the hydrochloride. The necessary γ -diethylaminopropylamine was prepared by reduction of β -diethylaminopropionitrile in ammoniacal methanol over Raney nickel, and was characterised by its picrate, picrolonate, and flavianate.

In connexion with other work on purine analogues, 5-amino-4:6-dihydroxy-2-methylpyrimidine (VII; R = NH₂) was required; this we proposed to prepare from 4:6-dihydroxy-2-methylpyrimidine (VII; R = H) *via* the 5-nitroso-derivative. Both the nitrosation of (VII;



R = H) and its reaction with *p*-chlorobenzenediazonium chloride have been described by Lythgoe, Todd, and Topham (*J.*, 1944, 315) but no attempt was made to isolate the products. On repeating these reactions, 5-*p*-chlorobenzenediazo-4:6-dihydroxy-2-methylpyrimidine (VII; R = N₂·C₆H₄·Cl) was obtained and characterised, but the bright green solid which separated on adding nitrous acid to the pyrimidine (VII; R = H) proved to be a dinitroso-compound, and not the expected derivative (VII; R = NO). In view of the reactivity of the 2-methyl group in certain hydroxypyrimidines, *e.g.*, 4-hydroxy-2-methylpyrimidine, which is oxidised by nitrous acid to 4-hydroxy-2-methylpyrimidine-2-carboxylic acid (Huber and Hölscher, *Ber.*, 1938, 71, 87), the product appeared to be 5-nitroso-4:6-dihydroxy-2-isonitrosomethylpyrimidine (VIII). The considerably increased yield obtained on using a second equivalent of nitrite supported this view, which was confirmed by reduction of the derivative to the corresponding diamine.

From the diaminopyrimidine (III) the triazolopyrimidine (IX; R = Me) was prepared by the action of nitrous acid, and was isolated as a hydrated double salt, C₆H₅ON₅·C₆H₄ON₅Na. As with the purine (V; R = NHPh), attempts to replace the 6-hydroxyl group by chlorine were unsuccessful. Roblin, Lampen, English, Cole, and Vaughan (*J. Amer. Chem. Soc.*, 1945, 67, 290) subsequently described the antibacterial activity of the lower homologue (IX; R = H), and when tested *in vitro* against *Staph. aureus* by the method of Heatley (*Lancet*, 1941, 2, 177), the 2-methyltriazole (IX; R = Me) was found to possess comparable activity.

Hydrochlorides of the amine (VI; R = NH·[CH₂]₃·NEt₂), and of the guanidine (IV; R = NH₂) and the analogous *p*-chloro-compound were tested against *P. gallinaceum* infections in chicks. The tests were kindly carried out by Miss I. M. Tonkin, National Institute of Medical Research, London, N.W. 3, who reports that none of the compounds has antimalarial activity.

EXPERIMENTAL.

4-Amino-5-(*N'*-phenylthiocarbamido)-6-hydroxy-2-methylpyrimidine (IV; R = SH).—4:5-Diamino-6-hydroxy-2-methylpyrimidine monohydrate (Traube, *Annalen*, 1923, 43, 287) (5 g., 1 mol.) in aqueous sodium hydroxide (1.43 g., 1.13 mol., in 25 c.c.), and a solution of ammonium phenyldithiocarbamate (*Org. Synth.*, 6, 72) (6.65 g., 1.13 mol.) in water (25 c.c.), were heated on a steam-bath for 6 hours. The precipitate, together with a further quantity of solid obtained by the addition of acid, was collected and purified by dissolving in 2*N*-sodium hydroxide. The phenylthiocarbamide (6.6 g., 76%) obtained on acidifying the filtered solution was crystallised from a large volume of boiling water, and formed

colourless microscopic tablets, m. p. $>310^\circ$ (Found : C, 52.5; H, 5.0; S, 10.8. $C_{12}H_{11}ON_4S$ requires C, 52.4; H, 4.7; S, 11.6%). The compound was insoluble in organic solvents, but dissolved readily in aqueous sodium hydroxide forming a mono-sodium salt and a more soluble di-sodium salt. It was not affected either by heating in boiling water for 48 hours, or on treatment with freshly prepared lead hydroxide in refluxing ethanol or isoamyl alcohol for 24 hours.

6-Hydroxy-8-mercapto-2-methylpyrimine (V; R = SH).—(a) The phenylthiocarbamide (IV; R = SH) (5 g.) was heated in boiling pyridine (50 c.c.) for 36 hours, and the solid collected and dissolved in 2*N*-sodium hydroxide. The micro-crystalline pale fawn powder obtained on acidification passed through filter paper, even after heating to 100° , and the product was accordingly isolated by centrifugation, and washed with water and ethanol. The resulting 6-hydroxy-8-mercapto-2-methylpyrimine, a light brown powder (2.7 g., 81%), m. p. $>310^\circ$, which was very sparingly soluble in water and organic solvents, was purified by precipitation from its aqueous alkaline solution with acid (Found : C, 39.4; H, 3.7; S, 17.4. $C_8H_8ON_4S$ requires C, 39.5; H, 3.3; S, 17.6%). It gave both a mono- and a di-sodium salt, the former being sparingly soluble.

(b) When 4 : 5-diamino-6-hydroxy-2-methylpyrimidine (5 g.) and excess of thiourea (10 g.) were fused over a flame for 30 minutes, the mixture frothed and evolved ammonia. After cooling, the mercaptopyrimine was extracted with dilute alkali, the purified product (4.95 g., 86%) being identical in appearance, solubilities, etc., with that from reaction (a) (Found : S, 17.0%).

6-Hydroxy-8-methylthio-2-methylpyrimine (V; R = SMe).—6-Hydroxy-8-mercapto-2-methylpyrimine (5 g.) in excess of 2*N*-sodium hydroxide was shaken at room temperature with methyl iodide (4.0 g., 1.1 mol.) for 20 minutes. On neutralisation, the methylthiopurine (4.3 g., 81%) separated in pale fawn needles, m. p. $>310^\circ$. The methyl ether is more soluble than the parent compound (V; R = SH), dissolving in both acids and alkalis and crystallising well from water (Found : C, 42.7; H, 4.4; N, 28.8; S, 16.4. $C_9H_{10}ON_4S$ requires C, 42.9; H, 4.1; N, 28.6; S, 16.3%).

On heating with aniline or γ -diethylaminopropylamine the methylthiopurine was either largely unchanged or, under extreme conditions, suffered decomposition.

4-Amino-5-(*N'*-phenylcarbamido)-6-hydroxy-2-methylpyrimidine (IV; R = OH).—4 : 5-Diamino-6-hydroxy-2-methylpyrimidine (7 g., 1 mol.), dried at $140^\circ/0.6$ mm. over phosphoric oxide, was heated with phenyl isocyanate (7 g., 1.17 mol.) in boiling toluene (100 c.c.) for 8 hours. The colourless solid product (11.5 g., 88.8%), which was very sparingly soluble in organic solvents, water, and acids, but readily soluble in alkalis, was crystallised from a large volume of boiling water. The pure phenylcarbamidopyrimidine formed colourless microscopic rhombs, m. p. $>305^\circ$ (Found : C, 55.2; H, 5.0; N, 26.5. $C_{12}H_{13}O_2N_6$ requires C, 55.6; H, 5.0; N, 27.0%).

Heating the derivative (2 g.) with phosphoryl chloride (10 c.c.), followed by removal of halide under reduced pressure, dissolution of the residue in ethanol, and precipitation with water, gave an uncrystallisable solid (1.2 g.) devoid of halogen. Prolonged treatment with phosphoryl chloride or phosphorus pentachloride in toluene gave inseparable mixtures of partly chlorinated products.

8-Anilino-6-hydroxy-2-methylpyrimine (V; R = NHPh).—(a) 4-Amino-5-(*N'*-phenylcarbamido)-6-hydroxy-2-methylpyrimidine (5 g.) in toluene (100 c.c.) was treated with phosphorus trichloride (1.8 g., 2 mol.), and the mixture refluxed for 10 hours. The solid was collected and purified by precipitation from its aqueous solution by addition of a large excess of concentrated hydrochloric acid. The purine (V; R = NHPh) was thus obtained as a sparingly soluble hydrochloride (4.6 g., 80.4%), crystallising in minute pale cream-coloured plates, m. p. $>310^\circ$ (Found : C, 46.2; H, 5.3; Cl, 12.0. $C_{12}H_{11}ON_4HCl \cdot 2H_2O$ requires C, 46.0; H, 5.1; Cl, 11.3%. Found, after drying at 100° : C, 50.0; H, 4.9. $C_{12}H_{11}ON_4HCl \cdot \frac{1}{2}H_2O$ requires C, 50.2; H, 4.5%).

(b) 4 : 5-Diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and phenylcyanamide were refluxed in dry *n*-butanol for 25 hours. The cooled product was filtered, thus giving a fawn solid (6 g.), which was extracted with hot water (300 c.c.). The undissolved halogen-free product (2.3 g., 33.5%) was soluble in alkalis and sparingly soluble in organic solvents. It was purified by adding a large excess of hydrochloric acid to its alkaline solution; the hydrochloride, m. p. $>310^\circ$, then separated in minute almost colourless plates (Found : C, 45.7; H, 5.1; N, 22.2; Cl, 11.1%. Found after drying at 100° : C, 50.0; H, 4.5%).

Evaporation of the solution from the hot water extraction gave only unchanged diaminopyrimidine hydrochloride. Yields from the above condensation varied considerably and were sometimes extremely small. Several attempts were made to obtain the 6-chloro-derivative from the purine (V; R = NHPh) using phosphorus chlorides, but only resinous products were obtained.

4-Amino-5-(*N'*-phenylguanidino)-6-hydroxy-2-methylpyrimidine (IV; R = NH_2).—Finely divided 4 : 5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (1.5 g.) and excess of phenylcyanamide (2 g.) were heated in boiling ethanol (60 c.c.) for 30 hours. The resulting solid (2.2 g., 83%) was collected and the guanidine purified as hydrochloride by crystallisation from dilute hydrochloric acid, from which the salt separated as small colourless plates, m. p. 295° (decomp.), soluble in alkali, very sparingly soluble in organic solvents (Found : C, 45.5; H, 5.6; N, 26.5; Cl, 11.6. $C_{12}H_{14}ON_6HCl \cdot H_2O$ requires C, 46.1; H, 5.4; N, 26.8; Cl, 11.4%. Found after drying at 100° : C, 47.2; H, 5.3. $C_{12}H_{14}ON_6HCl \cdot \frac{1}{2}H_2O$ requires C, 47.4; H, 5.3%).

On treating a solution of the pure hydrochloride with aqueous sodium picrate, the very sparingly soluble picrate separated as thick, minute yellow prisms, m. p. 270° (decomp.) (Found : C, 42.8; H, 3.9. $C_{12}H_{14}ON_6 \cdot C_6H_3O_7N_3 \cdot H_2O$ requires C, 42.7; H, 3.8%. Found after drying at 100° : C, 43.8; H, 3.9. $C_{12}H_{14}ON_6 \cdot C_6H_3O_7N_3$ requires C, 44.3; H, 3.5%).

Attempted ring-closure to (V; R = NHPh) by heating alone, or in high boiling solvents, or with concentrated hydrochloric acid, was unsuccessful.

***p*-Chlorophenylcyanamide.**—To *p*-chlorophenylthiourea (Stolle, *J. pr. Chem.*, 1932, 134, 282) (18.5 g., 1 mol.) and lead acetate (50 g., 1.5 mol.) in water (200 c.c.) at 90° a solution of potassium hydroxide (25 g., 4 mol.) was added. The mixture was shaken during 15 minutes' heating on a steam-bath, and, after removal of lead sulphide, the clear solution was cooled and acidified with acetic acid. *p*-Chlorophenylcyanamide separated as a colourless solid (9.4 g., 61%), insoluble in water, very

soluble in the common organic solvents, and crystallising from aqueous ethanol in long silky colourless needles, m. p. 107° (Found: C, 55.0; H, 3.2; Cl, 24.1. $C_7H_7N_4Cl$ requires C, 55.0; H, 3.3; Cl, 23.3%).

4-Amino-5-(N'-p-chlorophenylguanidino)-6-hydroxy-2-methylpyrimidine.—Finely powdered 4:5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and excess of *p*-chlorophenylcyanamide (10 g.) were refluxed in ethanol for 30 hours. The crystalline guanidine was collected and purified as the *dihydrochloride* by precipitation from an alkaline solution with hydrochloric acid. The salt formed a colourless microcrystalline powder, m. p. 302° (decomp.), virtually insoluble in organic solvents (Found: C, 39.4; H, 4.1; Cl, 29.4. $C_{12}H_{13}ON_6Cl_2 \cdot 2HCl$ requires C, 39.4; H, 4.1; Cl, 29.8%).

The *picrate*, which was precipitated from aqueous solutions of the hydrochloride and sodium picrate, crystallised from ethanol in minute yellow prisms, m. p. 268° (decomp.) (Found: C, 39.9; H, 3.6; N, 23.6. $C_{11}H_{13}ON_6Cl_2 \cdot C_6H_3O_7N_3 \cdot H_2O$ requires C, 40.2; H, 3.3; N, 23.4%).

6-N-Methylamino-8-methylthio-2-methylpurine (VI; R = NMePh).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with phosphoryl chloride (3.2 c.c.) and dimethylaniline (2 c.c.). The dark liquid was poured on ice, and after 1 hour the water layer was decanted and the residual tarry product triturated with a little ethanol. The crystalline residue (0.9 g., 22%) was the 6-methylamino-8-methylthio-2-methylpurine, which separated from alcohol-ether as a grey microcrystalline powder, m. p. 270–271° (decomp.), soluble in water, ethanol, and acetone, insoluble in ether (Found: C, 52.5; H, 6.2; Cl, 10.4. $C_{14}H_{15}N_5S \cdot HCl \cdot C_2H_5O$ requires C, 52.2; H, 6.0; Cl, 9.7%).

6-Chloro-8-methylthio-2-methylpurine (VI; R = Cl).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with excess of phosphoryl chloride. The thick black syrup remaining after evaporation was treated with sodium carbonate (2 g.), water (*ca.* $\frac{1}{2}$ c.c.), and toluene (50 c.c.), and the mixture heated to boiling. The hot toluene solution was decanted, and on cooling it deposited the *chloropurine* (1.75 g., 53%) in long colourless silky needles. The product was easily soluble in ethanol and almost insoluble in water. Crystallised from toluene, the pure compound had m. p. 231° (Found: C, 39.8; H, 3.5; Cl, 16.9. $C_7H_7N_4ClS$ requires C, 39.2; H, 3.3; Cl, 16.6%).

γ -Diethylaminopropylamine (cf. Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725).—Reduction of β -diethylaminopropionitrile (Holcomb and Hamilton, *ibid.*, 1942, **64**, 1309) (15 g.) in ammoniacal methanol (150 c.c. saturated at 0°) at 100°/100 atm. for 20 minutes gave γ -diethylaminopropylamine (12.3 g., 82%), b. p. 175°. It was identified by the picrate, m. p. 192° (decomp.) (literature 194°); the *picrolonate*, m. p. 261° (decomp.), a microcrystalline powder, very sparingly soluble in hot alcohol (Found: C, 49.4; H, 5.4. $C_7H_{18}N_2 \cdot 2C_{10}H_8O_6N_4$ requires C, 49.2; H, 5.4%; and the *flavinate*, yellow-orange, felted needles, m. p. 260° (decomp.), readily soluble in hot ethanol (Found: C, 45.8; H, 5.3. $C_7H_{18}N_2 \cdot C_{10}H_8O_6N_4 \cdot S$ requires C, 46.0; H, 5.4%).

6- γ -Diethylaminopropylamino-8-methylthio-2-methylpurine (VI; R = NH \cdot [CH $_2$] $_3$ ·NEt $_2$).—The hydroxypurine (VI; R = OH) (5 g.) was chlorinated as before, and the product remaining after removing excess of phosphoryl chloride was heated with γ -diethylaminopropylamine (5 g., 1.5 mol.) in boiling toluene (75 c.c.) for 10 hours. The solvent was evaporated under reduced pressure and the tarry residue extracted with ethanol (150 c.c.). Dry hydrogen chloride was passed into the extract and the volume reduced to 50 c.c. on a steam-bath. On cooling, the *purine hydrochloride* (14.5 g., 80%) separated as brown tablets, soluble in water, alcohol, and acetone; when recrystallised from ethanol-ether it formed colourless prisms, m. p. 243° (Found: C, 44.0; H, 6.9; N, 22.1; Cl, 19.2; S, 8.0. $C_{14}H_{24}N_6S \cdot 2HCl$ requires C, 44.1; H, 6.8; N, 22.1; Cl, 18.6; S, 8.4%).

On treating the above alcoholic extract with picric acid, the sparingly soluble *picrate* was obtained, which crystallised from alcohol as a monohydrate in yellow needles, m. p. 110° (decomp.) (Found: C, 40.3; H, 4.3; N, 21.0. $C_{14}H_{24}N_6S \cdot 2C_6H_3O_7N_3 \cdot H_2O$ requires C, 39.8; H, 4.1; N, 21.4%).

5-p-Chlorobenzeneazo-4:6-dihydroxy-2-methylpyrimidine (VII; R = N $_2$ ·C $_6$ H $_4$ ·Cl) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—A solution of *p*-chlorobenzene diazonium chloride, from *p*-chloroaniline (25 g.), in excess of hydrochloric acid was slowly added to 4:6-dihydroxy-2-methylpyrimidine (25 g.) in 2N-sodium carbonate (100 c.c.) containing excess of sodium acetate. The precipitated pale yellow solid (39.9 g., 76%) was collected and dried at 100°. The *pyrimidine* was sparingly soluble in organic solvents, but was crystallised from a large volume of ethanol, forming yellow needles, m. p. > 310°, which dissolved in alkali to an orange solution (Found: C, 50.0; H, 3.5. $C_{11}H_9O_2N_4Cl$ requires C, 49.9; H, 3.4%).

5-Nitroso-4:6-dihydroxy-2-isonitrosomethylpyrimidine (VIII) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—Sodium nitrite (5.5 g., 2 mol.) was added to the pyrimidine (VII; R = H) (5 g., 1 mol.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) dissolved in 2N-sodium hydroxide, and the mixture treated with excess of hydrochloric acid. A dark green solid immediately separated, which was collected and washed with alcohol and ether. The *dinitrosopyrimidine* (6.4 g., 89%) became grey at 100° but did not melt below 310° (Found: C, 32.2; H, 2.5. $C_8H_8O_4N_4$ requires C, 32.6; H, 2.2%). It was insoluble in organic solvents, but dissolved in aqueous alkali from which it was precipitated by acid. Repeated dissolution in alkali destroyed the characteristic green colour, and the pyrimidine was better purified through the *sodium salt*. This separated on the addition of alcohol to its aqueous solution as a bright green microcrystalline powder, m. p. > 310°, containing water of crystallisation (Found: C, 21.5; H, 2.6; N, 19.9. $C_8H_8O_4N_4 \cdot Na_2 \cdot 2\frac{1}{2}H_2O$ requires C, 22.0; H, 2.6; N, 20.5%. Found after drying at 100°: C, 24.1; H, 1.4. $C_8H_8O_4N_4 \cdot Na_2 \cdot H_2O$ requires C, 24.4; H, 1.6%).

5-Amino-4:6-dihydroxy-2-aminomethylpyrimidine.—The nitroso-compound (VIII) (11.5 g.) was added to aqueous ammonia (50 c.c. of 17%) saturated with hydrogen sulphide at 0°. After a few seconds the green colour disappeared, and a yellow solid was deposited, probably an ammonium salt. This was dissolved in hot water, and on acidifying with concentrated hydrochloric acid the diamine *hydrochloride* separated as a light pink powder (6.1 g., 42.6%), with decomposition point 200° (Found: C, 26.3; H, 4.8. $C_8H_8O_4N_4 \cdot 2HCl$ requires C, 26.2; H, 4.4%).

Both the hydrochloride and the free base are very soluble in water, sparingly soluble in organic solvents. Heating the base with water led to decomposition with elimination of ammonia.

5:6-(4:5-Triazole)-4-hydroxy-2-methylpyrimidine (IX; R = Me).—The *diaminopyrimidine* (III) (5 g.), dissolved in excess of hydrochloric acid, was treated at 0° with aqueous sodium nitrite (2.2 g. in 10 c.c.), and after 10 minutes the solution was carefully neutralised with solid sodium hydrogen carbonate.

The precipitated solid (3 g., 50%) crystallised from water in long plates, m. p. 310°, soluble in aqueous alkali and acid, and was found on analysis to consist of the triazolopyrimidine acid sodium salt *trihydrate* (Found: C, 31.4; H, 4.8; N, 37.0; Na, 6.1. $C_8H_8ON_3 \cdot C_8H_8ON_3 \cdot Na \cdot 3H_2O$ requires C, 31.7; H, 4.0; N, 37.0; Na, 6.1%). The compound was remarkably resistant to chlorinating agents, being almost quantitatively recovered even after fusion with phosphorus pentachloride.

The authors thank the Medical Research Council for the award of a grant to one of them (T. J. K.)

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[Received, October 8th, 1946.]

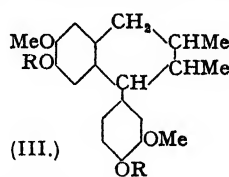
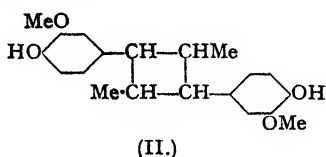
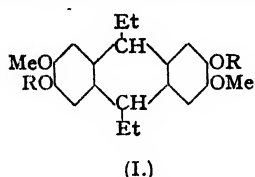
178. The Constituents of Natural Phenolic Resins. Part XXI.* The Structure of Diisoeugenol.

By NEVILLE J. CARTWRIGHT and ROBERT D. HAWORTH.

Structure (I; R = H) suggested for diisoeugenol in 1931 has been disproved by the synthesis of a tetramethoxyanthracene derivative of structure (I; R = Me) which, in its ready dehydrogenation, differs markedly from diisoeugenol dimethyl ether. Structure (III; R = H) is rejected because (a) such a lignan structure would be inconsistent with the difficulties experienced in the dehydrogenation of diisoeugenol derivatives, and (b) synthetic analogues of (III; R = Me) give colour reactions which differ from those shown by diisoeugenol dimethyl ether. Structure (IV; R = H) recently advanced by Müller *et al.* is regarded as the most likely structure for diisoeugenol for the following reasons. The ketone (VIII) has been synthesised and shown to be identical with the red oxidation product of diisoeugenol dimethyl ether which Haworth and Mavin (*J.*, 1931, 1363) had regarded as an anthrone derivative. The hydrindenes (IX) and (IV; R = Me) have been synthesised; both resist dehydrogenation and both give colour reactions resembling those exhibited by diisoeugenol dimethyl ether. The hydrindene (IV; R = Me) is, however, not identical with diisoeugenol dimethyl ether, but the difference may be stereochemical.

THE constitution of diisoeugenol has recently been the subject of eight communications by Müller *et al.* [(i) *Ber.*, 1942, 75, 692; (ii) *ibid.*, p. 891; (iii) *ibid.*, 1943, 76, 855; (iv) *ibid.*, p. 1061; (v) *ibid.*, p. 1119; (vi) *ibid.*, 1944, 77, 6; (vii) *ibid.*, p. 12; (viii) *ibid.*, p. 159] and as conclusions similar to our present views have been reached, it is desirable, in spite of the incomplete nature of our work, to place on record our contributions to this problem.

In 1931, Haworth and Mavin (*J.*, 1931, 1363) suggested that diisoeugenol had structure (I; R = H) instead of the cyclobutane structure (II) proposed by earlier workers. The introduction of this anthracene structure rested very largely on the isolation of 2 : 3 : 6 : 7-tetramethoxyanthraquinone from the products of the chromic acid oxidation of diisoeugenol dimethyl ether, but Szeki (*Annalen*, 1933, 507, 197) and Szeki and Haraszti (*ibid.*, 508, 294), disregarding



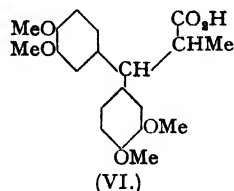
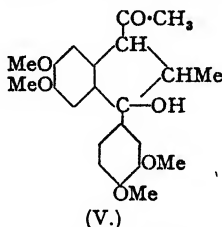
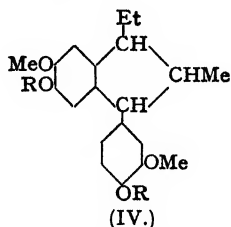
this evidence, adhered to the cyclobutane structure (II). Müller *et al.* [(i) and (ii)] first proposed the lignan structure † (III; R = H) but in later communications they abandoned this in favour of the hydrindene structure (IV; R = H) which resembles the metanethole structure suggested by Baker and Enderby (*J.*, 1940, 1094).

Müller's conclusions depend to a great extent upon the oxidation to *o*-veratroylveratric acid and upon the interpretation of the properties of a hydroxy-ketone obtained as one of the products of oxidation of diisoeugenol dimethyl ether. This substance, formulated as (V) in his later papers, is readily converted into a red anhydro-derivative, which is now regarded as an indene derivative, but for which Haworth and Mavin (*loc. cit.*) had tentatively proposed an anthrone structure. In our opinion Müller's work is inconclusive; the following observations made over a period of years, although equally inconclusive, have led us quite independently to the view that diisoeugenol is best represented by the hydrindene structure (IV; R = H).

* The last communication (*J.*, 1944, 535) of this series was erroneously numbered as Part XIX instead of Part XX.

† Oliverio (*Gazzetta*, 1943, 73, 270) reports that he suggested the lignan formula (III; R = H) for diisoeugenol in 1937.

In 1937, unpublished work with Miss W. Robson, B.Sc., showed that diisoeugenol dimethyl ether resembled 2 : 3 : 6 : 7-tetramethoxy-9 : 10-dihydroanthracene in absorption spectra, both

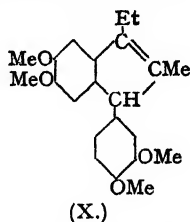
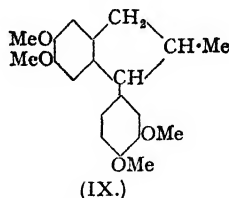
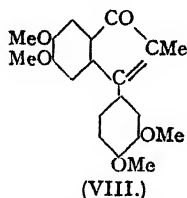
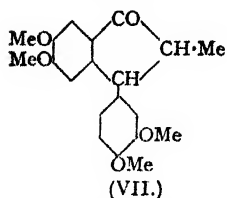


showing maximum absorption at a wave-length of 2850 Å., but structural similarity cannot be inferred, as the veratrole nuclei present in both structures are responsible for the absorption. At this stage, unsuccessful attempts were made to dehydrogenate diisoeugenol dimethyl ether with lead tetra-acetate, palladium black, and selenium and aluminium chloride, and numerous later efforts have been equally unsuccessful. The dihydroanthracene structure (I) can now be discarded, because Müller's observation that an anthracene derivative, and not a dihydroanthracene, is obtained by the condensation of veratrole and propaldehyde, indicates that dihydroanthracenes are characterised by an instability which is not shown by diisoeugenol dimethyl ether. In addition, we have reduced the highly fluorescent 2 : 3 : 6 : 7-tetramethoxy-9 : 10-diethylantracene by means of sodium and amyl alcohol to 2 : 3 : 6 : 7-tetramethoxy-9 : 10-diethyl-9 : 10-dihydroanthracene (I; R = Me), m. p. 148°. Unlike diisoeugenol dimethyl ether, this was readily dehydrogenated with lead tetra-acetate in glacial acetic acid solution to the corresponding anthracene derivative, and when a drop of concentrated nitric acid was added to its acetic acid solution a red coloration with a permanent blue reflex was obtained which differed from the cherry-red test given by diisoeugenol dimethyl ether.

Our failures, mentioned above, to dehydrogenate diisoeugenol dimethyl ether are equally inconsistent with the 1-phenyl-1 : 2 : 3 : 4-tetrahydronaphthalene structure (III); the expected product, dehydroguaiaretic acid dimethyl ether, is sparingly soluble in alcohol or acetic acid, and its isolation from complex selenium dehydrogenation mixtures has previously (J., 1938, 1681) been accomplished without difficulty. Attempts to synthesise the structure (III; R = Me) by the action of methyl-alcoholic hydrogen chloride, glacial acetic, and hydrochloric acid mixtures, 100% formic acid, sulphuric acid of various strengths, acetic and sulphuric acid mixture, or phosphoric oxide in toluene on guaiaretic acid dimethyl ether, have yielded unchanged materials, frequently in high yield but sometimes contaminated with intractable oils. Other routes investigated included: (a) the conversion of isolaricresinol dimethyl ether (J., 1937, 386) into the corresponding 2 : 3-bischloromethyl derivative for subsequent reduction; (b) dehydration and reduction of 4-hydroxy-6 : 7-dimethoxy-1-veratryl-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (J., 1938, 1681); (c) reduction of 6 : 7-dimethoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid (J., 1938, 811) and the isomeric 2-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-3-carboxylic acid (*loc. cit.*). These experiments gave either unchanged material or unrecognisable oils, and although these oils may contain diastereoisomeric forms of the structure (III; R = Me), it is unlikely that they contain the highly crystalline diisoeugenol dimethyl ether. In addition, 6 : 7-dimethoxy-1-veratryl-1 : 2 : 3 : 4-tetrahydronaphthalene, synthesised from veratrole and ethyl β-hydroxymethylene-propionate, gave colour reactions differing markedly from those of diisoeugenol dimethyl ether, and it was smoothly dehydrogenated by lead tetra-acetate to 6 : 7-dimethoxy-1-veratryl-naphthalene, m. p. 160° (J., 1935, 636).

These experiments led us to reject the dihydroanthracene and tetrahydronaphthalene structures (I) and (III), respectively, in favour of the hydrindene structure (IV), and synthetical confirmation of the latter has been sought. Condensation of veratrole and ethyl α-hydroxymethylenepropionate yielded ββ-diveratryl-α-methylpropionic acid (VI), m. p. 175°, and the corresponding acid chloride was converted into 5 : 6-dimethoxy-3-veratryl-2-methylhydrindone (VII), m. p. 116°. This cyclic ketone was dehydrogenated by heating with palladium at 250° to 5 : 6-dimethoxy-3-veratryl-2-methyl-1-indone (VIII), m. p. 194–195°, identical with the orange-red ketone which Haworth and Mavin (*loc. cit.*) previously regarded as 2 : 3 : 6 : 7-tetramethoxy-9-ethylantrone. The ketone (VII) was readily reduced by Clemmensen's method to give 5 : 6-dimethoxy-3-veratryl-2-methylhydrindene (IX), m. p. 117°. The ketone (VII) also reacted smoothly with ethylmagnesium iodide to yield the oily indene derivative (X), which combined

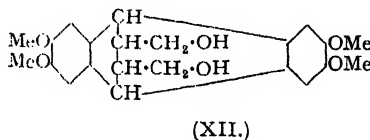
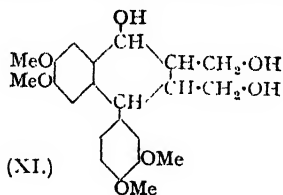
with excess Grignard reagent with the formation of a precipitate and the evolution of ethane. This reaction supports the indene structure (X) and excludes an alternative 1:3-dimethyldi-



hydronaphthalene formula arising from pinacolic change from the intermediate carbinol. The indene derivative (X) was reduced in acetic acid with a very active platonic oxide catalyst to give 5:6-dimethoxy-3-veratryl-2-methyl-1-ethylhydrindene (IV; R = Me), m. p. 105°, depressed to 95–98° by admixture with a specimen of diisoeugenol dimethyl ether, m. p. 105°. The hydrindene (IV; R = Me), like (IX) and diisoeugenol dimethyl ether, resisted dehydrogenation and gave a permanent cherry-red colour with a transient purple reflex when a drop of concentrated nitric acid was added to its solution in glacial acetic acid.

Structure (IV) permits of four racemic modifications. Ciamician and Silber (*Atti R. Accad. Lincei*, 1909, 18, 1216) converted the readily accessible form of diisoeugenol dimethyl ether, m. p. 105°, into an isomer, m. p. 96°, by the action of iodine, and Müller *et al.* (*loc. cit.*) have obtained a third isomer, m. p. 100°, by more indirect methods. These isomeric forms were not available for comparison purposes but the synthetic hydrindene derivative (IV; R = Me), m. p. 105°, is possibly an isomeric modification of diisoeugenol dimethyl ether, although efforts to convert it into a diastereoisomeric form by the action of methyl-alcoholic hydrogen chloride have failed.

The oxidation of diisoeugenol dimethyl ether to 2:3:6:7-tetramethoxyanthraquinone is in no way inconsistent with the hydrindene structure (IV; R = Me). Dreyfuss (*Gazzetta*, 1936, 66, 96) has shown that this anthraquinone, together with *o*-veratroylveratric acid and the lactone of 3:3':4:4'-tetramethoxybenzhydrol-6-carboxylic acid, is obtained by the oxidation of isoolivil dimethyl ether (XI). Structure (XII) is postulated as a possible intermediate stage in the conversion into the anthraquinone, and a similar mechanism could obviously be formulated for the oxidation of the hydrindene (IV; R = Me).



EXPERIMENTAL.

2:3:6:7-Tetramethoxy-9:10-diethyl-9:10-dihydroanthracene (I; R = Me).—2:3:6:7-Tetramethoxy-9:10-diethylanthracene (0.3 g.) (Müller, *loc. cit.*, ii) in boiling amyl alcohol (25 c.c.) was treated with sodium (2 g.). After $\frac{1}{2}$ hour's refluxing, water was added, the amyl alcohol was separated and dried, and the solvent removed under reduced pressure. Ethyl alcohol was added to the residue, and the unreduced anthracene derivative (0.15 g.) was collected and the filtrate concentrated; the 9:10-dihydroanthracene (I; R = Me) crystallised from methyl alcohol in colourless, dense prisms (0.06 g.), m. p. 147–148° (Found: C, 73.7; H, 7.9; OMe, 34.5. $C_{22}H_{24}O_4$ requires C, 74.1; H, 7.7; OMe, 34.8%), which gave the colour reaction described on p. 949.

Diacyl Derivatives of Guaiaretic and Dihydroguaiaretic Acids.—Crude extract (5 g.) of guaiacum resin, fused sodium acetate (5 g.), and acetic anhydride (15 c.c.) were heated on the water-bath for 2 hours. Water was added, and the product was collected and fractionally crystallised from ethyl alcohol. *Diacyl dihydroguaiaretic acid* separated from alcohol in stout irregular prisms, m. p. 112° (Found: C, 69.5; H, 7.1. $C_{24}H_{26}O_6$ requires C, 69.6; H, 7.3%), which gave no colouration with concentrated sulphuric acid. *Diacyl guaiaretic acid* separated from a small bulk of alcohol in slender hexagonal prisms, m. p. 86–87° (Found: C, 69.2; H, 6.8. $C_{24}H_{24}O_6$ requires C, 69.8; H, 6.8%), which gave a deep red colour with concentrated sulphuric acid and absorbed the theoretical amount of hydrogen.

6:7-Dimethoxy-1-veratryl-2-methyl-1:2:3:4-tetrahydronaphthalene-3-carboxylic Acid.—The conversion of the lactone of β -veratroyl- α -veratrylidene-*n*-butyric acid into methyl 6:7-dimethoxy-1-veratryl-2-methylnaphthalene-3-carboxylate (*J.*, 1938, 811) was best effected with methyl-alcoholic hydrogen chloride, saturated at 0°, and the methyl ester has m. p. 198° and not 178° as previously reported. The corresponding acid was reduced in faintly alkaline solution by boiling for 4 hours with 4% sodium amalgam (150 parts), during which time a stream of carbon dioxide was passed through the solution.

Acidification gave 6:7-dimethoxy-1-veratryl-2-methyl-1:2-dihydronaphthalene-3-carboxylic acid, which crystallised from methyl alcohol in clusters of fine needles, m. p. 178—179° (Found: C, 68.4; H, 6.4. $C_{22}H_{24}O_6$ requires C, 68.8; H, 6.3%), rapidly decolorising permanganate in cold alkaline solution. Reduction of this dihydro-acid was effected in acetic acid solution by hydrogen in presence of palladised charcoal; the corresponding tetrahydronaphthalene-3-carboxylic acid separated from methyl alcohol in silky needles, m. p. 162° (Found: C, 68.1; H, 6.9. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%), which were unaffected by cold permanganate. The corresponding acid chloride was not obtained pure, and Rosenmund reduction to the aldehyde was not realised.

4-Keto-6:7-dimethoxy-1-veratryl-1:2:3:4-tetrahydronaphthalene.—A mixture of concentrated sulphuric acid (11 c.c.) and glacial acetic acid (11 c.c.) was gradually added, with ice cooling, to a mixture of ethyl β -hydroxymethylcnepropionate (4 g.), veratrole (10 g.), and glacial acetic acid. After 18 hours, water was added and the product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (35 c.c.). Removal of the solvent and acidification gave the crude acid (9 g.) which was refluxed with excess of thionyl chloride in chloroform. The solvent was evaporated, the residue dissolved in nitrobenzene (50 c.c.), and aluminium chloride (8 g.) added. After 12 hours, dilute sulphuric acid was added, and the nitrobenzene removed in steam. The ketone, isolated with chloroform and washed with dilute sodium hydroxide, was distilled at 0.1 mm. (bath temp. 270°); the distillate (6 g.) crystallised from methyl alcohol in prisms, m. p. 137—138° (Found: C, 69.9; H, 6.5. $C_{20}H_{22}O_5$ requires C, 70.2; H, 6.4%), which gave a 2:4-dinitrophenylhydrazone, m. p. 270° (decomp.).

6:7-Dimethoxy-1-veratryl-1:2:3:4-tetrahydronaphthalene.—The above ketone (1 g.) was reduced by Clemmensen's method, and the product was distilled at 0.01 mm. and crystallised first from aqueous acetone and then from ligroin; clumps of fine needles, m. p. 76° (Found: C, 73.2; H, 7.3. $C_{20}H_{24}O_4$ requires C, 73.2; H, 7.3%), were obtained, which dissolved in concentrated sulphuric acid to give a bright red solution. When nitric acid was added to an acetic acid solution of the tetrahydronaphthalene, a reddish purple colour was obtained which gradually changed through blue and green to orange. Dehydrogenation with lead tetra-acetate in acetic acid solution gave 6:7-dimethoxy-1-veratryl-naphthalene, m. p. 160°.

$\beta\beta$ -Diveratryl- α -methylpropionic Acid (VI).—A mixture of concentrated sulphuric acid (32.5 c.c.) and glacial acetic acid (32.5 c.c.) was added to a cooled solution of ethyl α -hydroxymethylcnepropionate (13 g.) and veratrole (30 g.) in acetic acid (25 c.c.). After 12 hours the oily product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (100 c.c.). The acid (VI) crystallised from ethyl acetate in nodules of needles, m. p. 175° (Found: C, 66.7; H, 6.7; equiv., 362. $C_{20}H_{22}O_6$ requires C, 66.7; H, 6.7%; equiv., 360).

5:6-Dimethoxy-3-veratryl-2-methylhydrindone (VII).—The above acid (VI) (5.5 g.), in chloroform (50 c.c.), and thionyl chloride (3.5 g.) were refluxed for 1 hour, and the solvent removed in a vacuum. Aluminium chloride (5.5 g.) was gradually added with cooling to a solution of the residue in nitrobenzene (50 c.c.) and, after 12 hours, the mixture was decomposed and the nitrobenzene removed in steam. The product, isolated with ether and washed with sodium hydroxide solution, crystallised from methyl alcohol in large prisms (5 g.), m. p. 116° (Found: C, 69.9; H, 6.4. $C_{20}H_{22}O_6$ requires C, 70.1; H, 6.4%), yielding an oxime, which separated from methyl alcohol in long glistening needles, m. p. 149—150° (Found: C, 67.3; H, 6.4. $C_{20}H_{23}O_6N$ requires C, 67.2; H, 6.4%).

5:6-Dimethoxy-3-veratryl-2-methyl-1-indone (VIII).—The hydrindone (VII) (0.5 g.) and palladium black (0.1 g.) were heated for 1 hour at 250°, and the product was extracted with hot alcohol. Concentration of the extract gave orange-red prisms (0.05 g.), m. p. 189—192°, raised by recrystallisation from alcohol to 194—195°, unpressed by admixture with a specimen of the red compound, m. p. 193°, obtained by Haworth and Mavin (*loc. cit.*). The synthetic indone (VIII), and the product obtained by oxidation of diisoeugenol dimethyl ether, both dissolved in concentrated sulphuric acid to deep purple solutions.

5:6-Dimethoxy-3-veratryl-2-methylhydrindene (IX).—The hydrindone (VII) (4 g.) was reduced by Clemmensen's method; the product (3 g.) crystallised from methyl alcohol in long colourless needles, m. p. 117° (Found: C, 73.3; H, 7.4. $C_{20}H_{24}O_4$ requires C, 73.1; H, 7.3%) depressed to 102° when mixed with a specimen of the ketone (VII). The hydrinaene (IX) lacked ketonic properties, dissolved in concentrated sulphuric acid to a yellow solution, and gave the colour reaction described on p. 960. Dehydrogenation with selenium or lead tetra-acetate did not yield recognisable products.

5:6-Dimethoxy-3-veratryl-2-methyl-1-ethylindene (X).—The hydrindone (VII) (5 g.) in benzene (50 c.c.) was gradually added to a solution of ethylmagnesium iodide, prepared from magnesium (1.0 g.) and ethyl iodide (7.5 c.c.) in ether (50 c.c.). After decomposition with ice and ammonium chloride, the product was heated at 180° for $\frac{1}{2}$ hour with an equal weight of potassium hydrogen sulphate. The indene derivative (X), isolated with ether and washed with sodium bicarbonate solution, was obtained as a pale yellow resin, b. p. 195°/0.005 mm. (Found: C, 75.3; H, 7.7. $C_{22}H_{26}O_4$ requires C, 74.6; H, 7.4%), which reacted with ethylmagnesium iodide with formation of a precipitate and the evolution of ethane.

5:6-Dimethoxy-3-veratryl-2-methyl-1-ethylhydrindene (IV; R = H).—The indene derivative (X) (0.5 g.) in glacial acetic acid (10 c.c.) was shaken with hydrogen in the presence of freshly prepared Adams's platonic oxide catalyst (0.05 g.). The theoretical volume of hydrogen was absorbed in $\frac{1}{2}$ hour. After filtration from the catalyst, water was added and the product was isolated with ether, and washed with sodium bicarbonate solution. Removal of the ether left an oil which rapidly solidified and then crystallised from methyl alcohol in elongated prisms, m. p. 105° (Found: C, 74.0; H, 8.1. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%) depressed to 95—98° when mixed with diisoeugenol dimethyl ether.* The

* Note, added 12th October, 1946.—*Chemical Abstracts*, 1946, 40, pp. 5041—5043, which has just been received, contains summaries of two additional papers by Müller and his co-workers, but the original papers (*Ber.*, 1944, 77, 325, 343) are not available. In the second of these papers Müller describes the synthesis, by methods similar to ours, of the hydrindene (IV; R = Me), m. p. 105—106°. No mention of a direct comparison between the synthetic product and diisoeugenol dimethyl ether is included in the abstract, but, contrary to our observations, the title of the paper implies that identity is claimed.—R. D. H.

product, which did not decolorise permanganate in hot or cold acetone solution, was recovered after refluxing with methyl-alcoholic hydrogen chloride for $1\frac{1}{2}$ hours. It dissolved in concentrated sulphuric acid to an orange solution with a green fluorescence, and when a drop of concentrated nitric acid was added to its solution in glacial acetic acid, a red colouration with a purple reflex was obtained, which gradually changed to a pure cherry-red colour. Dehydrogenation with lead tetra-acetate in acetic acid or selenium at 280° yielded either unchanged material or unrecognisable tars.

Our thanks are due to the West Riding Education Committee for a Scholarship.

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[Received, October 14th, 1946.]

179. *Substituted Benzilic Acids and Benzophenones.*

By A. H. FORD-MOORE.

A method for preparing substituted benzilic acids is described. Since these acids can be oxidised smoothly to the corresponding benzophenone, a number of the latter compounds which cannot be prepared by the Friedel-Crafts method are made available. The ethochlorides of the dimethylaminoethyl esters of some of these acids have been prepared, and their mydriatic activity measured against atropine sulphate.

IN a recent paper (Ford-Moore and Ing, this vol., p. 55), a number of synthetic mydriatics was described. One of these compounds, benzilyloxyethyl dimethylethylammonium chloride (I; $R_1 = R_2 = \text{Ph}$), for which the name "Lachesine" has been suggested, was found to have a mydriatic activity equal to that of atropine sulphate. Certain other compounds in which



substituents were introduced into the benzene nuclei of (I) were also prepared but were not then described. The result of this substitution was to reduce greatly, or even to abolish, the mydriatic activity of the compound.

This paper describes the preparation of the substituted benzilic acids used. These are mainly symmetrically disubstituted acids, but two monosubstituted acids were prepared and are included.

Two methods are available for the preparation of benzilic acids; oxidation of a benzoin with bromate and alkali, and treatment of a benzil with aqueous-alcoholic potash. Since the benzoin acids of substituted benzaldehydes could not usually be made to solidify, whereas the corresponding benzils were highly crystalline, the second method was adopted. Most of the substituted benzils are, however, so sparingly soluble in aqueous-alcoholic potash that conversion into the benzilic acid either takes place very slowly or not at all. Since these acids decarboxylate somewhat readily to give the benzhydrol, it is not safe to prolong the potash treatment for more than ten minutes.

Rearrangement of the substituted benzils can be brought about very readily by heating for ten minutes or less with a 20% solution of potassium hydroxide in hot *n*-butanol. In certain cases, the potassium salt of the acid separates out and only requires to be filtered off, washed with a little ether, dissolved in water, and acidified. Where the potassium salt is soluble in butanol, it can be extracted with water, a little ether being added to facilitate separation into two layers.

When the aqueous solution of the potassium salt is acidified, there is a strong tendency for the acid to separate in an obstinately gummy condition. Crystallisation can usually be induced by adding a small amount of a suitable solvent (benzene or petrol) and scratching. Seed, if available, will greatly hasten solidification.

The substituted benzilic acids are oxidised smoothly and in good yield by chromic anhydride in acetic acid to the corresponding benzophenone (cf. Jena, *Annalen*, 1870, **155**, 83). A number of the latter compounds, which cannot be prepared by the usual Friedel-Crafts method, are therefore made available.

Two monosubstituted benzilic acids, *viz.*, phenyl- α -naphthyl- and phenyl- β -naphthylglycollic acids, were described by Ford-Moore and Ing (*loc. cit.*). The same method as had been used for preparing these acids, *viz.*, *via* the deoxybenzoin, the isonitroso-derivative, and the benzil, was adopted for preparing phenyl-*p*-tolylglycollic acid and 4-chlorobenzilic acid. The monosubstituted benzils, obtained in the penultimate step, are much more soluble in aqueous-alcoholic potash than are the disubstituted benzils, and no difficulty was experienced in converting them into the corresponding benzilic acids by means of this reagent.

Mydriatics from Substituted Benzoic Acids.—These compounds were made by the same method as was used for preparing (I), *i.e.*, treatment of β -chloroethyltrimethylammonium chloride with the potassium salt of the acid in ethanol (Ford-Moore and Ing, *loc. cit.*). The compounds so obtained were useless as mydriatics. Nevertheless, they serve to illustrate the striking decrease in mydriatic activity on introducing substituents into the benzilyloxy-moiety of (I).

EXPERIMENTAL.

2:2'-Dimethoxybenzoic Acid.—*o*-Anisil (2:2'-dimethoxybenzil) (35 g.) was added to a solution of potassium hydroxide (17 g.) in boiling *n*-butanol (90 c.c.), and the mixture refluxed for 10 minutes. After cooling, the mixture was extracted three times with 100-c.c. portions of water, some ether being added to facilitate separation into two layers. The combined aqueous extracts were extracted once with ether (50 c.c.) to remove any dissolved butanol, freed from ether with a current of air, and acidified to Congo-red with hydrochloric acid. The *dimethoxybenzoic acid* was precipitated as a sticky mass which, if it did not solidify rapidly, could be made to do so by decanting the water, adding about 20 c.c. of benzene, and scratching. The yield was 33 g., m. p. 160°, after crystallising from methanol (Found: C, 66.4; H, 5.5. $C_{10}H_{10}O_5$ requires C, 66.6; H, 5.6%).

Piperonic (3:4:3':4'-bismethylenedioxybenzoic) acid, m. p. 139° from ethyl acetate (Found: C, 61.0; H, 4.0. $C_{16}H_{12}O_8$ requires C, 60.8; H, 3.8%), 4:4'-dimethoxybenzoic acid, m. p. 171° (decomp.), from methanol (Böslér, *Ber.*, 1881, 14, 327, gives 164°) (Found: C, 66.35; H, 5.7. Calc. for $C_{16}H_{12}O_5$: C, 66.6; H, 5.6%), and 3:3'-dichlorobenzoic acid, m. p. 110° from benzene-petrol (Klimont, Diss., Heidelberg, 1891, gives 114–115°) (Found: C, 56.4; H, 3.4. Calc. for $C_{14}H_8O_2Cl_2$: C, 56.55; H, 3.35%), were prepared similarly. The last compound was rather reluctant to crystallise but could be made to do so by adding petrol (b. p. 40–60°) and scratching.

5:5'-Dibromo-2:2'-dimethoxybenzoic Acid.—The corresponding benzil (cf. Kuhn, Birkofer, and Möller, *Ber.*, 1943, 76, 903), m. p. 231° (20 g.), was treated with potash-butanol (7 g.; 40 c.c.) as for the dimethoxybenzil. On cooling, the potassium salt of the acid separated. It was filtered off, washed free from butanol with ether, and freed from ether by standing in the air for a short time. It was dissolved in water and acidified with hydrochloric acid; yield, 18 g., m. p. 181°, after crystallising from methanol (Found: C, 42.9; H, 3.25. $C_{16}H_{10}O_5Br_2$ requires C, 43.1; H, 3.15%).

Veratric (3:3':4:4'-tetramethoxybenzoic) acid was prepared similarly; it melted at 131° after crystallising from ethyl acetate (Vanzetti, *Atti R. Accad. Lincei*, 1936, 24, II, 468, gives ca. 68°) (Found: C, 61.9; H, 5.8. Calc. for $C_{18}H_{20}O_7$: C, 62.05; H, 5.8%).

These acids show a tendency to undergo partial decarboxylation. The benzhydrol so formed is difficult to remove by recrystallisation. Purification is readily effected by dissolution in dilute sodium carbonate solution, filtration (carbon), acidification, and crystallisation from a suitable solvent.

2:2'-Dimethoxybenzophenone.—2:2'-Dimethoxybenzoic acid (21.5 g.) was dissolved in boiling glacial acetic acid (100 c.c.) and oxidised by gradual addition of powdered chromic anhydride (5.5 g.). The reaction proceeded without the application of heat. When it was complete (10 mins.), the mixture was poured into water. The ketone, which rapidly solidified, was filtered off and washed free from chromium salts successively with water, dilute sodium carbonate, and water; yield 15 g., m. p. 103°, after crystallising from methanol (Graebe and Feer, *Ber.*, 1896, 19, 2610, give 104°; Richter, *J. pr. Chem.*, 1883, 28, 287, gives 98°).

3:3':4:4'-Tetramethoxybenzophenone, m. p. 147° from ethanol (Kostanecki and Tambor, *Ber.*, 1906, 39, 4027, give 145°), **5:5'-dibromo-2:2'-dimethoxybenzophenone**, m. p. 128° (Diels and Rosenmund, *ibid.*, p. 2362, give 123°), and **3:3'-dichlorobenzoic acid**, m. p. 123–124° from methanol (Found: C, 62.3; H, 3.5. $C_{18}H_{14}OCl_2$ requires C, 62.2; H, 3.2%), were prepared similarly from the appropriate benzoic acid.

4-Chlorobenzoic acid and **phenyl-*p*-tolylglycollic acid** were prepared by the method described in the text. The former melted at 131° (Found: C, 64.1; H, 4.45. $C_{14}H_{11}O_2Cl$ requires C, 64.0; H, 4.2%), and the latter at 132° (Weiss, *Monatsh.*, 1919, 40, 396, gives 131–133°), both having been crystallised from benzene.

Colour with Concentrated Sulphuric Acid.—The benzoic acids described above gave the following colours with concentrated sulphuric acid: 2:2'-dimethoxy-, brilliant greenish-blue; 4:4'-dimethoxy-, brilliant bluish-green; 3:3':4:4'-tetramethoxy-, brilliant bluish-green; 3:4:3':4'-bis-methylenedioxy-, dark greenish-brown; 5:5'-dibromo-2:2'-dimethoxy-, brilliant bluish-green; 3:3'-dichloro-, violet; 4-chloro-, orange-red; phenyl-*p*-tolylglycollic acid, dark reddish-brown.

*Dimethylaminoethyl ester ethochlorides and their mydriatic activity.**

Serial number.	In (I) : R ₁ = R ₂ =		M. p.†	Analysis, %.				
				Found :		Reqd. :		
				C.	H.	C.	H.	R.M.P.‡
E19	3 : 4-CH ₃ O ₂ C ₆ H ₃		225° (d.)	58.30	5.77	58.46	5.80	0
E18	<i>p</i> -OMe·C ₆ H ₄	<i>p</i> -OMe·C ₆ H ₄	136°	62.54	7.28	62.36	7.08	8
E20	<i>m</i> -Cl·C ₆ H ₄	<i>m</i> -Cl·C ₆ H ₄	218—220° (d.)	55.61	5.50	55.50	5.59	0
E24	<i>p</i> -Me·C ₆ H ₄	Ph	189—190°	67.00	7.44	66.75	7.47	16
E23	<i>p</i> -Cl·C ₆ H ₄	Ph	196—197°	60.33	6.37	60.32	6.33	0

* Cf. Ford-Moore and Ing (*loc. cit.*).

† The solvent used for recrystallisation was ethanol-acetone.

‡ Relative molar potency (atropine sulphate = 100) on mouse eye.

The microanalyses were carried out by Mr. W. Brown and by Messrs. Weiler and Strauss.

The work described in this paper, which is published by permission of the Director General of Scientific Research (Defence), Ministry of Supply, was carried out while the author was a member of Sir Robert Robinson's team in the Dyson Perrins Laboratory, Oxford.

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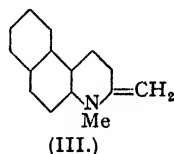
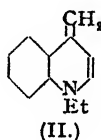
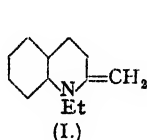
[Received, October 23rd, 1946.]

180. Some Heterocyclic Methylene Bases and their Anilomethyl Derivatives.

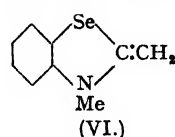
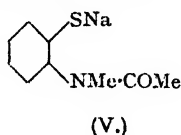
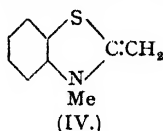
By FRANCES M. HAMER, RUSSELL J. RATHBONE, and BARBARA S. WINTON.

Some heterocyclic methylene bases, not hitherto described in the solid state, have been prepared by the action of alkali on quaternary salts at a low temperature, foregoing extraction. Some new anilomethyl derivatives of bases of this type were prepared by the action of alkali on quaternary salts having a 2- β -anilinoethyl group. They include anilomethyl derivatives of methylene bases derived from a benzoxazolium salt and a thiazolium salt, although the unsubstituted bases of these series are not precipitable. A practical method of preparation of ethylisoformanilide is described. These compounds were made as starting materials for the synthesis of neocyanine and related dyes.

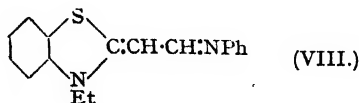
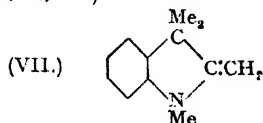
By treating quinaldine ethiodide with aqueous alkali, Vongerichten and Höfchen obtained an oil, which they regarded as the methylene base (I); they showed that it reacted with quinoline ethiodide to give a cyanine dye (*Ber.*, 1908, **41**, 3054). König expressed the opinion that bases such as (I) and (II) play an essential part in the formation of cyanines (*Ber.*, 1922, **55**, 3293).



Mills and Raper, considering that the oils formed by the action of alkali on quinaldine alkiodides could not be obtained analytically pure, examined the crystalline product (III) (*J.*, 1925, **127**, 2466); this led Rosenhauer (with Hoffmann and Unger) to record his preparation of the methyl analogue of (I) (*Ber.*, 1926, **59**, 946). From 2-methylbenzthiazole methoperchlorate König and Meier obtained (IV) (*J. pr. Chem.*, 1925, **109**, 324). Clark studied the conditions favouring formation of this base or of the thiophenol salt (V) and similarly, from 2-methylbenzselazole methiodide, obtained two products, one of which was (VI) (*J.*, 1928, **2313**).



All these methylene bases were prepared from known quaternary salts but (VII), the first to be known, was made by direct synthesis (Fischer and Steche, *Annalen*, 1887, **242**, 348; Brunner, *Ber.*, 1898, **31**, 612).



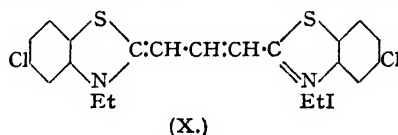
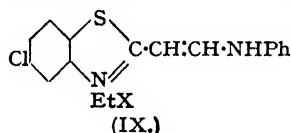
In our work on the synthesis of neocyanines, the methylene bases are of interest as starting points. In the patent literature Brooker and White have described anilomethyl derivatives, e.g. (VIII), of some such bases (Kodak Ltd., B.P. 561,172/1940) and these also have the same interest. The present paper deals with methylene bases and their anilomethyl derivatives.

Success in preparing methylene bases, hitherto inaccessible in the solid state, was achieved by precipitating them at a low temperature, by the action of alkali on a solution of the quaternary salt, and foregoing extraction with a solvent. We began by making the ethyl analogue of (IV), choosing a readily soluble quaternary salt of 2-methylbenzthiazole; it was

liable to manifest its instability by decomposing during drying but we succeeded in recrystallising both it and its 5-chloro-derivative. Its 6:7-benz-derivative showed a greater tendency to decompose and was not recrystallised; in preparing this and the ethyl analogue of (VI), aqueous suspensions of the quaternary salts were performed in place of concentrated solutions. From concentrated solutions of alko-*p*-toluenesulphonates, (I) and (II) were prepared. Colour changes, which indicate reactivity and tendency to cyanine dye formation on the part of the bases, occurred before they could be filtered off but did not proceed progressively after they had been dried.

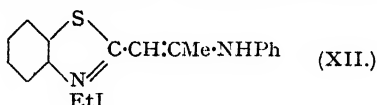
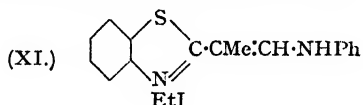
Quaternary salts of certain other heterocyclic bases that are of interest in cyanine dye condensations do not give precipitates of methylene bases when their cold solutions are treated with alkali; such are salts of 2-methylbenzoxazole, 2:4-dimethylthiazole, 2-methylthiazoline, and α -picoline. In the different series of salts it appears that there is more than one cause for this. In the pyridine series, the base may possibly be too soluble and more complex methylene bases of this series have in fact been prepared (Mumm and Hingst, *Ber.*, 1923, 56, 2301). In the benzoxazole series, it is due to fission of the ring, as recognised by König and Meier (*J. pr. Chem.*, 1925, 109, 324).

In preparing the anilomethyl derivative (VIII) of the ethyl analogue of (IV) from 2- β -anilinoethylbenzthiazole ethiodide, the method of the patent (Kodak Ltd., B.P. 561,172/1940) was adopted with some modification. In preparing 5-chloro-2- β -anilinoethylbenzthiazole ethiodide (IX; X = I), in order to make the 5-chloro-analogue of (VIII), the salt was accompanied by so much *thiacarbocyanine* (X) as by-product that we were forced, in order to get rid of the dye, first to isolate the pure 5-chloro-analogue of (VIII), from which we prepared the pure *ethochloride* (IX; X = Cl), and ultimately from that the pure *ethiodide* (IX; X = I). We prepared the 6-nitro-derivative of (VIII), starting from the product of nitration of 2-methylbenzthiazole



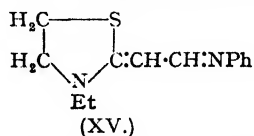
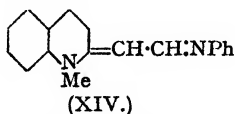
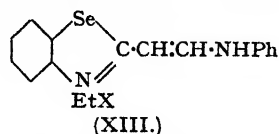
(Browning, Cohen, Ellingworth, and Gulbransen, *Proc. Roy. Soc.*, 1931, B, 108, 119; for orientation of the nitration product see Brooker, Keyes, and Williams, *J. Amer. Chem. Soc.*, 1942, 64, 199). The 6-nitro-2-methylbenzthiazole was converted into its *metho-p-toluenesulphonate*; this was condensed with ethylisoformanilide (cf. Knott, *J.*, 1946, 120), and the resultant salt treated with alkali to give the desired base.

To synthesise the α -methyl derivative of (VIII), 2-ethylbenzthiazole, prepared by two hitherto unpublished methods, was converted into its *etho-p-toluenesulphonate* and this was condensed with diphenylformamidine, or better with ethylisoformanilide, and the product treated with



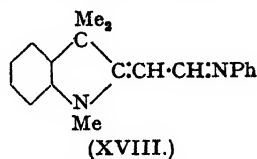
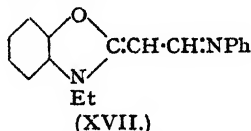
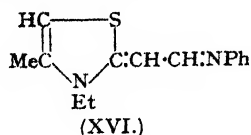
potassium iodide to give (XI), whence the base was liberated by the action of alkali. We also prepared the β -methyl derivative of (VIII) by the action of alkali on the quaternary salt (XII).

In the preparation of the selenium analogue of (VIII), from the quaternary salt (XIII; X = I), the product refused to solidify, but after treatment with hydrochloric acid to give the *ethochloride* (XIII; X = Cl) it was possible to obtain the solid base by the action of alkali. In the quinoline series we prepared (XIV), the ethyl analogue of which has been described (Kodak Ltd., B.P. 561,172/1940). Particularly interesting is the record in the patent that the anilomethyl derivative of a methylene base of the thiazoline series was prepared, since the



unsubstituted methylene base of this series is one of those not precipitable by the action of alkali on the quaternary salt. We were also able to prepare the corresponding ethyl analogue (XV), by applying different conditions, and the anilomethyl derivatives, (XVI) and (XVII), of

methylene bases of a thiazole series and of the benzoxazole series, respectively, where again the parent unsubstituted bases have not been described.



To obtain the *anilomethyl* derivative (XVIII) of the methylene base (VII), 2- β -anilino-3:3-dimethylindolenine methiodide was acted on, in benzene suspension, by aqueous alkali. The quaternary salt was originally prepared either by hydrolysing the corresponding acetanilidovinyl compound or else by heating 1:3:3-trimethylindolenine methiodide with diphenylformamidine (I.C.I. Ltd., Piggott, and Rodd, B.P. 344,409/1929), but we used ethylisoformanilide instead of diphenylformamidine.

Ethylisoformanilide was required for the present work and also for our synthesis of neocyanine, so that its large-scale production became a matter of interest. Claisen's methods for preparing it were to condense ethyl orthoformate (1) with aniline, (2) with diphenylformamidine, or (3) with formanilide in the presence of aniline hydrochloride (*Annalen*, 1895, 287, 362). Monier-Williams (*J.*, 1906, 89, 273) preferred to use the method of Comstock and Kleeburg (*Amer. Chem. J.*, 1890, 12, 497) and treated dry silver isoformanilide with ethyl iodide in absolute ether. This last did not seem practicable on a large scale and we worked out a modification of Claisen's first method, including aniline hydrochloride in order to inhibit the formation of carbylamine.

EXPERIMENTAL.

3-Ethyl-2-methylenebenzthiazoline.—2-Methylbenzthiazole etho-*p*-toluenesulphonate (50 g.; 1 mol.) was dissolved in water (70 c.c.). The solution was cooled with ice and stirred during the addition of a cold solution of sodium hydroxide (6.3 g.; 1.1 mols.) in water (20 c.c.). The white solid was filtered off, and well washed with ice-cold water. It was dried in a vacuum desiccator and obtained in 83% yield (21 g.), being pale pink at this stage. Once dry, it kept for weeks without further deterioration but preparations on a larger scale were apt to decompose during drying. On recrystallisation from light petroleum (b. p. 80–100°; 20 c.c. per g.), the yield was 62%. After drying in a vacuum desiccator, it was analysed by the method of Carius, which method was used throughout this work (Found: S, 18.15. $C_{10}H_{11}NS$ requires S, 18.1%; m. p. 126–128° (decomp.)).

5-Chloro-3-ethyl-2-methylenebenzthiazoline.—Similarly, 5-chloro-2-methylbenzthiazole etho-*p*-toluenesulphonate gave the base in 87% yield; on recrystallisation from light petroleum (b. p. 80–100°; 275 c.c. per g.), it fell to 57% (Found, after drying in a vacuum desiccator: Cl, 16.45; S, 15.1. $C_{10}H_{10}NClS$ requires Cl, 16.75; S, 15.15%). The chalky white solid had m. p. 178–180° (decomp.).

3-Ethyl-2-methylene-6:7-benzbenzthiazoline.—2-Methyl-6:7-benzbenzthiazole etho-*p*-toluenesulphonate (30 g.; 1 mol.) was ground to a paste with ice-cold water (30 c.c.), and an ice-cold solution of sodium hydroxide (3.3 g.; 1.1 mols.) in water (10 c.c.) was added. The sulphur-yellow solid was thoroughly washed with ice-cold water and was obtained in 68% yield (11.65 g.) (Found: S, 14.55. $C_{16}H_{13}NS$ requires S, 14.1%); it was liable to change overnight to a sticky mass at the early stages of drying but, once past those early stages, could be kept unchanged in a vacuum desiccator. When heated, shrinking and darkening began about 40° and it was brown and sticky by 50°; gradual melting and decomposition occurred, and by 90° it was a brown liquid.

3-Ethyl-2-methylenebenzthiazoline.—2-Methylbenzthiazole ethiodide when similarly treated gave a 76% yield of base. Selenium was determined as silver selenite (Becker and Meyer, *Ber.*, 1904, 37, 2550) (Found: Se, 35.45. $C_{10}H_{11}NSe$ requires Se, 35.3%). The yellowish-brown powder softened from 70° and decomposed at about 120°. One specimen, which had been kept for several days in a vacuum desiccator without change, became sticky and dark overnight, although the vacuum had been maintained.

1-Ethyl-2-methylene-1:2-dihydroquinoline (I).—Quinaldine etho-*p*-toluenesulphonate (34.33 g.; 1 mol.), dissolved in ice-cold water (30 c.c.), was treated with ice-cold aqueous sodium hydroxide solution (4.4 g., 1.1 mols., in 11 c.c.). The buff precipitate was filtered off and thoroughly washed with ice-cold water. After drying in a vacuum desiccator, it was obtained in 78% yield (13.37 g.), and was then brick-red (Found: N, 7.95. $C_{15}H_{13}N$ requires N, 8.2%); m. p. 79° (decomp.) with previous softening. A sample which had been kept in a vacuum desiccator for a fortnight appeared to be unchanged.

1-Ethyl-4-methylene-1:4-dihydroquinoline (II).—Lepidine (14.31 g.; 1 mol.) and ethyl *p*-toluenesulphonate (20.02 g.; 1 mol.) were heated together in an oil-bath at 155–160° for 3 hours. A solution of the viscous salt in water (32 c.c.) was extracted with ether, then treated ice-cold with a solution of sodium hydroxide (4.4 g.; 1.1 mols.) in water (11 c.c.). The precipitate was filtered off and well washed with ice-cold water. The filtrate became deep blue. After drying in a vacuum desiccator, the yield of pale blue solid was 73% (12.55 g.) (Found: N, 8.2. $C_{12}H_{13}N$ requires N, 8.2%). It had no definite m. p. On heating, shrinking began at 59°; in one case, with slow heating, it was black and molten by 80°, whilst in another, violent frothing occurred between 95° and 108°.

3-Ethyl-2-aniloethylidenbenzthiazoline (VIII).—The published method (Kodak Ltd., B.P. 561,172/1940) was varied in that the suspension of 2- β -anilino-3:3-dimethylbenzthiazole ethiodide (103 g.; 1 mol.) in acetone (940 c.c.) was shaken with a solution of sodium hydroxide (31 g.; 3 mols.) in water (75 c.c.), instead of

being stirred mechanically. In one instance solution occurred, but in another, very much more acetone (11.4 l.) had to be added, this indicating the conversion of a less stable into a more stable form. The acetone extracts were filtered, with removal of bis-2-(3-ethylbenzthiazole)trimethincyanine iodide (5.81 g.), which was recrystallised from methyl alcohol (75 c.c. per g.; 2.7 g. obtained) and dried in a vacuum at 60–80°, which conditions of drying were used throughout this work, except where otherwise stated (Found: I, 25.95. Calc. for $C_{21}H_{18}N_2IS_2$: I, 25.8%). On pouring the acetone filtrate into its own volume of water, the base was precipitated in 70% yield (49 g.). Two recrystallisations from light petroleum (b. p. 80–100°; 100 c.c. per g.) reduced the yield to 43% (Found, after drying in a vacuum desiccator: S, 11.25. Calc. for $C_{21}H_{18}N_2S$: S, 11.45%). The yellow solid had m. p. 79°, whereas the m. p. quoted in the patent is 98–99° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3935 Å. and of one containing sulphuric acid at 4175 Å.

5-Chloro-3-ethyl-2-aniloethylidenbenzthiazoline.—5-Chloro-2-methylbenzthiazole ethiodide (20 g.; 1 mol.) and ethylisoformanilide (7 g.; 1 mol.) were heated together with stirring at 140–150° for 1 hour. The product was boiled with spirit (300 c.c.), and the crystals were filtered off after cooling (22 g. obtained). An attempt to separate the quaternary salt from the dye by-product by boiling out five times with spirit (2×100 c.c., 2×150 c.c., 250 c.c.) left a dye residue (5.69 g.), and a 36% yield (9.43 g.) of impure salt crystallised from the extracts. The dye was further boiled out twice with methyl alcohol (50 c.c., 100 c.c.) and the residue (4.96 g.) suspended in acetone (38 c.c.) and shaken with a solution of sodium hydroxide (1.35 g.) in water (5 c.c.), with the object of converting any contaminating salt into base. After two more acetone extractions, the residual dye was well washed with water (3.46 g. obtained) and recrystallised from methyl alcohol (1590 c.c.) (2.81 g. obtained) (Found: $2Cl + I$, 35.45. $C_{21}H_{18}N_2Cl_2IS_2$ requires $2Cl + I$, 35.25%). The blue needles of bis-2-(5-chloro-3-ethylbenzthiazole)trimethincyanine iodide (X) did not melt below 270°. The absorption maximum was at 5625 Å. It sensitised a gelatino-bromide photographic emulsion from 5200 to 6200 Å., with a maximum at 6000 Å. The impure quaternary salt (9.43 g.; 1 mol.) was suspended in acetone (70 c.c.), and the ice-cold solution shaken with one of sodium hydroxide (2.56 g.; 3 mols.) in water (10 c.c.). The acetone extract was filtered and the aqueous part further extracted with acetone, dye by-product being left undissolved. The extracts were precipitated with thrice their volume of water and the resultant solid was obtained in 83% yield (5.57 g.). After recrystallisation from methyl alcohol (335 c.c.) the yield was 70% (Found: Cl , 11.45. $C_{21}H_{18}N_2ClIS$ requires Cl , 11.3%). The yellowish-green powder had m. p. 138°. The absorption maximum of a methyl-alcoholic solution containing pyridine was at 4075 Å. and of one containing sulphuric acid at 4205 Å. The dye sensitised a chloride emulsion to 4900 Å. with the maximum at 4600 Å.

5-Chloro-2-β-anilinovinylbenzthiazole Ethochloride (IX; X = Cl).—5-Chloro-3-ethyl-2-aniloethylidenbenzthiazoline (6.64 g.) was warmed with spirit (13 c.c.), and the suspension treated with concentrated hydrochloric acid (7 c.c.). The crystals which separated on cooling (7.49 g.) were recrystallised from methyl alcohol (60 c.c.) and obtained in 86% yield (6.36 g.) (Found: Cl , 20.2. $C_{21}H_{18}N_2Cl_2S$ requires Cl , 20.2%). The bright yellow powder became orange at 100°, was brown by 200°, and melted at 214–215° (decomp.).

5-Chloro-2-β-anilinovinylbenzthiazole Ethiodide (IX; X = I).—The ethochloride (IX; X = Cl) (0.45 g.; 1 mol.) was dissolved in hot spirit (15 c.c.) and added to a hot solution of potassium iodide (16.6 g.; 10 mols.) in water (30 c.c.). The crude salt (0.47 g.) was recrystallised from methyl alcohol (47 c.c. per g.) and obtained in 58% yield (0.33 g.) (Found: $Cl + I$, 36.8. $C_{21}H_{18}N_2ClIS$ requires $Cl + I$, 36.7%). The dark orange crystals had m. p. 241–244° (decomp.).

6-Nitro-2-methylbenzthiazole Metho-p-toluenesulphonate.—6-Nitro-2-methylbenzthiazole (2.77 g.; 1 mol.) and methyl p-toluenesulphonate (2.66 g.; 1 mol.) were heated together at 130° for 1 hour, and the product was ground with absolute ether (5.16 g. obtained; 95%). After recrystallisation from absolute ethyl alcohol (10 c.c.), the yield was 88% (4.77 g.) (Found: S, 16.8. $C_{21}H_{16}O_4N_2S_2$ requires S, 16.85%). The cream-coloured crystals had m. p. 194–195° (decomp.).

6-Nitro-2-β-anilinovinylbenzthiazole Metho-p-toluenesulphonate.—The foregoing metho-p-toluenesulphonate (19 g.; 1 mol.) and ethylisoformanilide (9 g.; 1.2 mols.) were heated and stirred together at 130–140°. Fusion occurred, then vigorous reaction followed by solidification. Heating was continued for $\frac{1}{2}$ hour. A suspension of the solid in spirit (50 c.c.) was poured into warm water. The product, after being washed with water and with acetone (18 g. obtained), was recrystallised from methyl alcohol (200 c.c. per g.), the yield falling from 75% to 23% (Found: S, 13.45. $C_{23}H_{21}O_4N_3S_2$ requires S, 13.25%). The green crystals had m. p. 255°.

6-Nitro-3-methyl-2-aniloethylidenbenzthiazoline.—The preceding compound (9.66 g.; 1 mol.), acetone (300 c.c.), and 20% sodium hydroxide solution (20 c.c.; 5 mols.) were warmed together on the steam-bath, then shaken vigorously for several minutes. The filtered acetone layer was concentrated to one-third, and poured into ice and water (500 c.c.), coagulation being assisted by addition of ammonium chloride. The washed product (4.83 g.; 78%) was purified by dissolving in benzene (10 c.c. per g.), filtering, and precipitating with an equal volume of light petroleum (b. p. 80–100°); yield, 63% (Found: S, 10.45. $C_{23}H_{21}O_4N_3S$ requires S, 10.3%). The brick-red crystals had m. p. 144° (decomp.) and desensitised strongly. The broad absorption curve of a methyl-alcoholic solution containing ammonia had its maximum at 3850 Å.

2-Ethylbenzthiazole.—This was originally prepared by heating o-aminothiophenol in a sealed tube with propionyl chloride, being characterised as its platinichloride (Hofmann, *Ber.*, 1880, **13**, 8). According to our first method, o-aminothiophenol hydrochloride (80.6 g.; 1 mol.) was treated with propionic anhydride (69.5 c.c.; 1.1 mols.) and with zinc dust (11.2 g.). The reaction was started by warming; after it had subsided, the mixture was heated on the steam-bath for 2 hours, and then made alkaline with sodium hydroxide and steam-distilled; the oil was extracted with chloroform, and the extract dried (Na_2SO_4). After removal of the solvent, the residue was distilled in a vacuum and obtained in 52% yield, b. p. 127–131°/6 mm. (Found: S, 19.8. Calc. for C_8H_9NS : S, 19.65%). Our second method consisted in preparing o-aminothiophenol from o-chloronitrobenzene (cf. I. G. Farbenind. A.-G., F.P. 669,921/1929; Société Anonyme des Matières Colorantes, et Produits Chimiques de Saint-

Denis, F.P. 714,682/1930) and effecting the ring closure to 2-ethylbenzthiazole by means of propionic anhydride. *o*-Chloronitrobenzene (100 g.; 1 mol.), crystalline sodium sulphide (400 g.; 2.63 mols.), and water (400 c.c.) were stirred together, being warmed to start the reaction; after its vigour had abated, heating on the steam-bath and stirring were continued for 4 hours. The mixture was steam-distilled to remove *o*-chloroaniline, formed as a by-product (26 g.; 32%), then it was cooled, treated with a solution of propionic anhydride (83 g.; 1 mol.) in propionic acid (156 g.; 3.3 mols.), and heated under reflux for an hour on the steam-bath. It was cooled, made alkaline and extracted with ether. The extract was dried (Na_2SO_4), the solvent removed, and the residue distilled under a vacuum. After a second vacuum distillation the yield was 34% (35 g.), b. p. 112–114°/5 mm. (Found: S, 19.9%). The preparation according to the first method was carried out by Miss E. M. Wilson, and that according to the second by Mr. J. Fraser.

2-Ethylbenzthiazole Etho-*p*-toluenesulphonate.—2-Ethylbenzthiazole (4.08 g.; 1 mol.) and ethyl *p*-toluenesulphonate (5 g.; 1 mol.) were heated together at 140–150° for 2½ hours. The solidified melt was ground and washed with acetone, being obtained in 84% yield (7.55 g.) (Found: S, 17.8. $\text{C}_{18}\text{H}_{21}\text{O}_2\text{NS}_2$ requires S, 17.65%). The pale pink solid melted at 138°.

2-(β -Anilino- α -methylvinyl)benzthiazole Ethiodide (XI).—The preceding compound (5 g.; 1 mol.) and ethylisoformanilide (2.3 g.; 1.1 mols.) were heated together at 120–140°, vigorous reaction then occurring. Heating was continued for ½ hour, and the red liquid was dissolved in spirit (7 c.c.) and treated with a hot solution of potassium iodide (8.26 g.; 4 mols.) in water (7 c.c.). The iodide crystallised and, after being washed, was obtained in 72% yield (4.3 g.), decreased on recrystallisation from ethyl alcohol (50 c.c. per g.) to 50% (Found: I, 30.1. $\text{C}_{18}\text{H}_{19}\text{N}_2\text{IS}$ requires I, 30.05%). The dull red crystals melted at 212° (decomp.).

When a similar preparation was carried out with diphenylformamidine instead of ethylisoformanilide, the yield of crude washed product was only 24%. Neither diphenylformamidine nor ethylisoformanilide gave a positive result when the starting point was 2-ethylbenzthiazole ethiodide instead of the etho-*p*-toluenesulphonate.

3-Ethyl-2-aniloisopropylidenebenzthiazoline.—2-(β -Anilino- α -methylvinyl)benzthiazole ethiodide (5.44 g.; 1 mol.), 20% sodium hydroxide solution (12 c.c.; 5 mols.), and acetone (150 c.c.) were stirred together and warmed on the water-bath, then shaken in a separating funnel. The filtered acetone layer was poured into ice-water. The aqueous liquid was decanted from the sticky solid, which on crystallisation from light petroleum (b. p. 80–100°; 75 c.c.) gave a 41% yield (1.57 g.) of yellow crystals, m. p. 92° (decomp.) (Found after drying in a vacuum at 50–60°: S, 10.85. $\text{C}_{18}\text{H}_{19}\text{N}_2\text{S}$ requires S, 10.9%). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4005 Å. The compound sensitised a chloride emulsion fairly strongly with its maximum at 4550 Å., sensitisation extending to 4850 Å.

2-(β -Anilino- β -methylvinyl)benzthiazole Ethiodide (XII).—The steps in the following synthesis of the salt required as starting point were carried out according to directions supplied by Dr. L. G. S. Brooker: 2-methylbenzthiazole etho-*p*-toluenesulphonate was converted successively into 3-ethyl-2-acetylmethylenebenzthiazoline (Kodak Ltd., B.P. 466,269/1935), 2- β -chloropropenylbenzthiazole ethochloride (*idem*, B.P. 533,425/1939), 3-ethyl-2-thioacetylbenzthiazoline (*idem*, B.P. 546,705/1941), and 2-(β -methylthiopropenyl)benzthiazole etho-*p*-toluenesulphonate (*idem*, B.P. 538,857/1941). This last salt (66.1 g.; 1 mol.), aniline (19.7 g.; 1.25 mols.), and absolute alcohol (170 c.c.) were boiled together under reflux for 30 minutes. The yellowish-brown solution was poured into a hot solution of potassium iodide (56 g.; 2 mols.) in water (100 c.c.). The iodide was obtained in 84% yield (60.0 g.). On recrystallising twice from spirit (15 c.c. per g.), the yield dropped to 69% (Found: I, 30.25. $\text{C}_{18}\text{H}_{19}\text{N}_2\text{IS}$ requires I, 30.05%). The bright yellow crystals had m. p. 203° (decomp.).

3-Ethyl-2- β -anilopropylidenebenzthiazoline.—2-(β -Anilino- β -methylvinyl)benzthiazole ethiodide (8.44 g.; 1 mol.), suspended in acetone (250 c.c.), was stirred and warmed for a few minutes on the steam-bath with 20% sodium hydroxide solution (20 c.c.; 5 mols.), and the mixture shaken. The filtered acetone layer was poured into ice-cold water (1000 c.c.). The solid (5.5 g.) was recrystallised from light petroleum (b. p. 80–100°; 25 c.c. per g.), the yield then being 65% (3.85 g.) (Found: S, 10.7. $\text{C}_{18}\text{H}_{19}\text{N}_2\text{S}$ requires S, 10.9%). The pale yellow crystals had m. p. 114° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3670 Å. The base was photographically inert.

2- β -Anilino- β -vinylbenzthiazoline Ethiodide (XIII; X = I).—2-Methylbenzthiazole ethiodide (28.2 g.; 1 mol.) and ethylisoformanilide (13.2 g.; 1.1 mols.) were heated together at 150–160° for ½ hour. The product was ground with spirit (32.7 g. obtained); after recrystallisation from spirit (30 c.c. per g.) the yield was 59% (Found: I, 27.8. $\text{C}_{17}\text{H}_{17}\text{N}_2\text{ISe}$ requires I, 27.85%). The greenish-golden crystals had m. p. 222° (decomp.).

3-Ethyl-2-anilooctylidenebenzthiazoline.—The above ethiodide (32 g.; 1 mol.), ground to a paste with water, was treated with 40% sodium hydroxide solution (40 c.c.; 5 mols.) and acetone (500 c.c.). The mixture was slightly warmed, then well shaken. The filtered, concentrated acetone extract gave with dilute hydrochloric acid 2- β -anilino- β -vinylbenzthiazoline ethochloride (XIII; X = Cl), which, after recrystallisation from acetone-spirit (3:1, 30 c.c. per g.), was obtained in 55% yield (14.4 g.). Chlorine was determined by the method which has been found suitable for iodine in the presence of selenium (Hamer, *Analyst*, 1933, 58, 26) (Found: Cl, 9.55. $\text{C}_{17}\text{H}_{17}\text{N}_2\text{ClSe}$ requires Cl, 9.75%). The bright yellow crystals had m. p. 205° (decomp.). They were dissolved in hot spirit, and the base precipitated by dilute ammonia (11.2 g.; 49%); it was recrystallised from light petroleum (b. p. 80–100°; 20 c.c. per g.) and the yield was 34% (7.8 g.) (Found: N, 8.55. $\text{C}_{17}\text{H}_{17}\text{N}_2\text{Se}$ requires N, 8.55%). The bright yellow crystals had m. p. 96°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3940 Å. and of one containing sulphuric acid at 4235 Å. For a chloride emulsion the base was a medium sensitiser, with the maximum at 4600 Å., sensitisation extending to 5100 Å.

1-Methyl-2-anilooctylidenedihydroquinoline (XIV).—2- β -Anilino- β -vinylquinoline methiodide (7.76 g.; 1 mol.) was suspended in acetone (100 c.c.) and shaken for 12 minutes with a solution of sodium hydroxide (4 g.; 5 mols.) in water (50 c.c.). The filtered acetone layer with ice-cold water (600 c.c.) deposited the base in 97% yield (10.16 g.). On recrystallising from light petroleum (b. p. 80–100°)-benzene (1:1,

10 c.c. per g.), some tar was left undissolved and the yield fell to 62% (Found, after drying in a vacuum desiccator: N, 10.95. $C_{18}H_{16}N_2$ requires N, 10.75%). The bright orange crystals had m. p. 88° (decomp.). The absorption maximum of an alkaline methyl-alcoholic solution was at 4335 Å. In a gelatino-chloride photographic emulsion, sensitisation extended to 5100 Å., with a maximum at 4700 Å.

3-Methyl-2-aniloethylidenethiazolidine.—This was prepared from 2-β-anilinovinylthiazoline methiodide and sodium hydroxide in aqueous acetone, followed by precipitation with water, as described (Kodak Ltd., B.P. 561,172/1940). The yield was 79%, dropping to 73% on recrystallisation from benzene (1 c.c. per g.) (Found, after drying to constant weight in a vacuum desiccator: S, 14.6. Calc. for $C_{18}H_{16}N_2S$: S, 14.7%). The m. p. was 79–80°, whereas that published is 99–100°.

3-Ethyl-2-aniloethylidenethiazolidine (XV).—2-β-Anilinovinylthiazoline ethiodide (36 g.; 1 mol.), benzene (800 c.c.), and 40% sodium hydroxide solution (80 c.c.; 8 mols.) were heated together under reflux on a steam-bath, with vigorous stirring, for 30 minutes. After the solvent had been distilled from the filtered benzene layer, the solid residue was recrystallised from light petroleum (b. p. 80–100°; 1000 c.c.) and obtained in 77% yield (18.0 g.) (Found, after drying in a vacuum desiccator: S, 13.75. $C_{18}H_{16}N_2S$ requires S, 13.8%). The cream-coloured substance had m. p. 65°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3585 Å. with an inflexion to the curve at 3200 Å.; one containing sulphuric acid had its maximum at 3660 Å. On a gelatino-chloride photographic emulsion it conferred extra-sensitivity up to 4400 Å.

4-Methyl-3-ethyl-2-aniloethylidene-Δ⁴-thiazoline (XVI).—4-Methyl-2-β-anilinovinylthiazole ethiodide (18.6 g.; 1 mol.) was ground with 20% sodium hydroxide solution (50 c.c.; 4 mols.). The mixture was stirred and warmed with acetone (250 c.c.). The crude product (23 g.), obtained by precipitation of the acetone layer with ice-water (1000 c.c.), was recrystallised from light petroleum (b. p. 80–100°) and benzene (2 : 1, 20 c.c. per g.). A 74% yield of golden crystals (18.0 g.) was obtained (Found: S, 12.95. $C_{18}H_{16}N_2S$ requires S, 13.1%; m. p. 122° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4090 Å. and of one containing sulphuric acid at 4030 Å. The substance sensitised a chloride emulsion fairly strongly, sensitisation extending to 4900 Å., with the maximum at 4500 Å.

3-Ethyl-2-aniloethylidenebenzoxazoline (XVII).—2-β-Anilinovinylbenzoxazole ethiodide (58.8 g.; 1 mol.), aqueous 40% sodium hydroxide solution (90 c.c.; 6 mols.), and benzene (1500 c.c.) were stirred together and warmed gently on a steam-bath, then shaken vigorously for several minutes. The benzene solution was filtered and distilled down to dryness: the resultant gum was taken up with acetone, and the base precipitated with water, being obtained in 58% yield (23 g.). Recrystallisation was difficult; benzene appeared to be the most suitable solvent (5 c.c. per g.) but the yield fell to 6% (Found, after drying in a vacuum desiccator: N, 10.5. $C_{17}H_{14}ON_2$ requires N, 10.6%). The pale yellow crystals had m. p. 65° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3660 Å. and of one containing sulphuric acid at 3835 Å. A gelatino-chloride photographic emulsion was weakly sensitised to 4400 Å., with the maximum effect at 4200 Å.

3 : 3-Dimethyl-2-β-anilinovinylindolenine Methiodide.—2 : 3 : 3-Trimethylindolenine methiodide (20 g.; 1 mol.) and ethylisoformanilide (10 g.; 1 mol.) were heated together in an oil-bath at 140° for 40 minutes with continual breaking up of the lumpy solid. After dissolving in hot spirit (130 c.c.), the product crystallised in 75% yield (20 g.). It was boiled out with spirit (25 c.c.) and on recrystallising the residue from spirit (125 c.c.) the yield was 55% (Found: I, 31.35. Calc. for $C_{19}H_{21}N_2I$: I, 31.4%). The yellow crystals had m. p. 236–238° (decomp.).

1 : 3 : 3-Trimethyl-2-aniloethylideneindoline (XVIII).—The foregoing methiodide (3.91 g.; 1 mol.) was suspended in benzene (40 c.c.) and shaken with a solution of sodium hydroxide (1.16 g.; 3 mols.) in water (5 c.c.). Subsequently four more such benzene extractions were carried out. The benzene filtrate was taken to dryness and the residue twice recrystallised from light petroleum (b. p. 80–100°; 2 × 8 c.c.), the yields being 73% and 64% (1.70 g.) (Found, after drying in a vacuum desiccator: N, 10.0. $C_{19}H_{20}N_2$ requires N, 10.15%). The yellow powder had m. p. 89°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3745 Å. and of one containing sulphuric acid at 4120 Å. It sensitised a gelatino-chloride photographic emulsion up to 4700 Å.

Ethylisoformanilide.—Ethyl orthoformate (1200 c.c.; 2 mols.), aniline (336 c.c.; 1 mol.), and aniline hydrochloride (36 g.) were boiled together in an oil-bath for 4 hours, in a flask fitted with fractionating column, condenser, and receiver to collect the alcohol eliminated. The temperature of the bath was kept at 120° until the first vigour of the reaction had subsided and was then raised to 140–150°. After cooling, any diphenylformamidine was filtered off, and the filtrate was fractionally distilled under a vacuum. After a forerun, b. p. 50–110°/20 mm., the ethylisoformanilide was collected at 110–120°/20 mm. The foreruns from several batches were fractionated together, the fraction boiling up to 110°/20 mm. being used as ortho-ester for another preparation, and the fraction above 110°/20 mm. being refractionated with ethylisoformanilide. As a result, the 85% yield from a second fractional distillation (504 g.) is slightly larger than that from the first fractionation (81% yield; 480 g.).

We are indebted to Miss M. D. Gauntlett for the absorption spectra, to Dr. B. H. Carroll and Dr. E. B. Knott for the photographic tests, and to Mr. J. Fraser and Miss E. M. Wilson for the preparations specified.

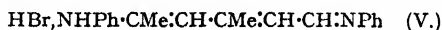
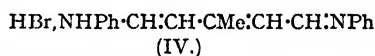
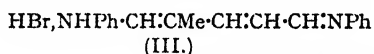
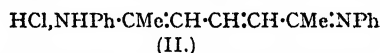
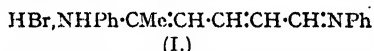
181. Symmetrical Tricarbocyanines having One or More Methyl Groups as Substituents on the Chain.

By FRANCES M. HAMER and RUSSELL J. RATHBONE.

1-, 2-, and 3-Methyl derivatives of glutamic aldehyde dianilide hydrohalide were prepared, also 1:5- and 1:3-dimethyl derivatives, from the appropriate pyridinium cyanobromides. They were condensed with heterocyclic quaternary salts to give tricarbocyanines having β -, γ -, and δ -methyl groups, also $\beta\beta'$ - and $\beta\delta$ -dimethyl groups on the chain. Absorption maxima and photographic sensitising action of the dyes are recorded.

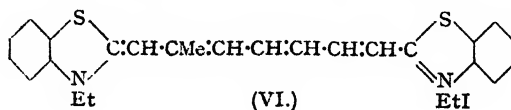
In a patent on photographic sensitising action, the four examples of chain-substituted tricarbocyanines comprise one with a β -methyl and three with a δ -methyl group (I.G. Farbenind. A.-G., B.P. 394,537/1931). It is recorded that the intermediate for the first was prepared by König's method from β -naphthylamine, α -picoline, and cyanogen chloride in ether (*J. pr. Chem.*, 1904, 69, 105), whilst that for the others was obtained analogously from aniline, γ -picoline, and cyanogen bromide. As no preparations whatever are described, we considered it desirable to record some.

Although König did originally describe the preparation of a dye from α -picoline, cyanogen chloride, and *o*-toluidine (*loc. cit.*), he subsequently disclaimed it but claimed that pure β -picoline does indeed form such a dye (*J. pr. Chem.*, 1904, 70, 19). König and Schreckenbach (*ibid.*, 1913, 87, 241) had found that 2:4-dinitrophenylpyridinium chloride does not, whilst pyridinium cyanobromide does, react with indoles to give dyes. α -Picoline and $\alpha\alpha'$ -lutidine do not combine with 1-chloro-2:4-dinitrobenzene to give pyridinium salts but we made them react with cyanogen bromide and thence, with aniline and hydrobromic or hydrochloric acid, obtained dyes (I) and (II). Similarly from β -picoline we prepared (III), referred to (but not described) by König (*ibid.*, 1904, 70, 19), and from γ -picoline we prepared (IV). The product derived from γ -lutidine was used in condensations but we did not isolate a pure specimen of (V).



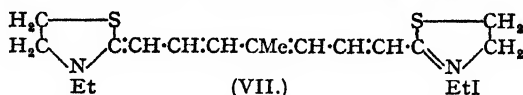
We compared the absorption maxima of (I)–(IV) in methyl-alcoholic solution with that of the parent dye having an unsubstituted chain. In passing from the parent dye to (II) and (III), there were bathochromic shifts of the maximum, of 45 Å. and 10 Å., respectively, and hypsochromic shifts, of 90 Å. and 65 Å., respectively, in passing to (I) and (IV). Whereas the parent dye is a photographic sensitiser, (I) was distinctly weaker, whilst (II), (III), and (IV) showed no sensitising power.

Glutamic aldehyde dianilide hydrohalide condenses in the presence of sodium ethoxide, or of sodium acetate in acetic anhydride, with quaternary salts having reactive methyl groups to give tricarbocyanines (Fisher and Hamer, *J.*, 1933, 189), but these condensing agents seemed unsuitable for use with the present substituted intermediates. However, Brooker had used piperidine at a low temperature (Kodak Ltd., B.P.P. 436,941/1933; 437,017/1933), and this method proved applicable here. By thus condensing 2-methylbenzthiazole ethiodide, with (I), (III), (IV), (II), and the crude (V), respectively, there resulted the β -methylthiatricarbocyanine (VI), which has been already described (I.G. Farbenind. A.-G., B.P. 394,537/1931), and



the corresponding γ - and δ -methyl-, and $\beta\beta'$ - and $\beta\delta$ -dimethyl-thiatricarbocyanines. By condensing 5:6-dimethoxy-2-methylbenzthiazole ethiodide and 2-methyl-6:7-benzbenzthiazole ethiodide, respectively, with (II), the 5:6:5':6'-tetramethoxy- and 6:7:6':7'-dibenz-derivatives of the $\beta\beta'$ -dimethylthiatricarbocyanine were prepared. The dye obtained by condensing 2-methyl-6:7-benzbenzthiazole ethiodide with (IV) has already been described (*idem, ibid.*). By condensing 2-methylbenzselenazole ethiodide with (II), (III), and (IV), respectively, there resulted a $\beta\beta'$ -dimethyl-, and a γ - and a δ -methyl-selenatricarbocyanine.

Condensation of (IV) and (V), respectively, with 2-methylthiazoline ethiodide gave the *8-methylthiazolinocarbocyanine* (VII) and the corresponding $\beta\delta$ -dimethyl compound.



We compared the absorption maxima in methyl-alcoholic solution of the chain-substituted tricarbocyanines with the corresponding parent dyes: the figures are shown in the accompanying table. In one instance, introduction of a β -methyl group caused a bathochromic shift of 60 Å. Introduction of a γ -methyl group caused a bathochromic shift of 5 Å. and a hypsochromic shift

Chain.	Thia-	Absorption (Å.) of tricarbocyanine iodides:			
		Tetramethoxythia-	Dibenzthia-	Selena-	Thiazolino-
Unsubstituted	7620 *	8000	7970 *	7700 *	6450 †
β -Me	7680	—	—	—	—
γ -Me	7610	—	—	7705	—
δ -Me	7900	—	8250	8000	6750
$\beta\beta'$ -Me ₂	7720	7900	8290	7970	—
$\beta\delta$ -Me ₂	7060	—	—	—	6585

* Fisher and Hamer, *Proc. Roy. Soc.*, 1936, A, 154, 703.

† Fisher and Hamer, *J.*, 1933, 189.

of 10 Å. Introduction of a δ -methyl group had a more profound effect; thus, in four instances this caused consistently a bathochromic shift, the values being 280, 280, 300, and 300 Å. The introduction of $\beta\beta'$ -dimethyl groups caused a hypsochromic shift of 100 Å. in one case, but bathochromic shifts, of 100, 320, and 270 Å., respectively, in three others. $\beta\delta$ -Dimethyl groups produced a hypsochromic shift of 560 Å. and a bathochromic shift of 135 Å.

These chain-substituted tricarbocyanines comprise photographic sensitisers but, as already noted for symmetrical dicarbocyanines carrying a methyl group on the chain (Hamer and Rathbone, *J.*, 1945, 595), it cannot be said that they are in general better than the parent dyes with an unsubstituted chain.

EXPERIMENTAL.

1-Anilino-5-anilo-1-methyl-1:3-pentadiene Hydrobromide (I).—Cyanogen bromide (5 g.; 1 mol.) was added to water (30 c.c.) which was cooled with ice. Aniline (10 c.c.; >2 mols.) was added and α -picoline (5 c.c.; 1 mol.) was gradually stirred in. After 30 minutes in ice, the mixture was gradually treated with ice-cold hydrobromic acid (14 c.c., *d* 1.45; 2.5 mols.). After standing in the cold overnight, the red solid was filtered off and ground once with water (20 c.c.) and thrice with acetone (19% yield; 3.00 g.). This and the other pentadiene derivatives were dried in a vacuum desiccator before analysis (Found: Br, 23.25. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{Br}$ requires Br, 23.3%). The maroon crystals had m. p. about 155° (decomp.), depending on the rate of heating. Their absorption maximum was at 4760 Å. whereas the corresponding substance with an unsubstituted chain had its maximum at 4870 Å. They sensitised a gelatino-bromide photographic emulsion weakly up to 5700 Å.

1-Anilino-5-anilo-1:5-dimethyl-1:3-pentadiene hydrochloride (II) was similarly prepared from aniline (10 c.c.), cyanogen bromide in ice-cold water, and α -lutidine, followed by concentrated hydrochloric acid. The solid was filtered off, ground with water (40 c.c.) and thrice with acetone (40 c.c. \times 2, 60 c.c.). The yield (7.28 g.) was 25% (Found: Cl, 11.3. $\text{C}_{19}\text{H}_{21}\text{N}_2\text{Cl}$ requires Cl, 11.3%). The red crystals had m. p. 150–151° (decomp.). The absorption maximum was at 4915 Å. and the dye had no photographic sensitising action.

1-Anilino-5-anilo-2-methyl-1:3-pentadiene hydrobromide (III) was similarly prepared from cyanogen bromide (5 g.) in cold water with aniline and β -picoline, followed by hydrobromic acid. The yield of washed hydrobromide was 37% (Found: Br, 22.8. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{Br}$ requires Br, 23.3%). The maroon crystals had m. p. about 148° but dependent on the rate of heating. The absorption maximum was at 4880 Å. The dye did not sensitise. In another experiment more hydrobromic acid (another 2.5 mols.) was added and produced a pale pink solid. It was filtered off and washed with acetone (2.4 g. obtained; 9% yield) and appeared to be the *dihydrobromide*, m. p. 239° (decomp.) (Found: Br, 37.75. $\text{C}_{18}\text{H}_{20}\text{N}_2\text{Br}_2$ requires Br, 37.7%). The hydrochloride was similarly prepared.

1-Anilino-5-anilo-3-methyl-1:3-pentadiene Hydrobromide (IV).—To cyanogen bromide (5 g.; 1 mol.) in water (10 c.c.), with slight cooling, was added a mixture of γ -picoline (5 c.c.; 1 mol.) and aniline (10 c.c.; >2 mols.). A vigorous reaction occurred with rise of temperature. Hydrobromic acid was stirred in (14 c.c., *d* 1.45; 2.5 mols.), followed quickly by ice-water. The yield of washed solid was 6.65 g. (31%), and this was used in condensations. On recrystallising a sample from methyl alcohol (50 c.c. per g.) the yield was 13% (Found: Br, 23.2. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{Br}$ requires Br, 23.3%). The dark maroon crystals had m. p. 167° (decomp.). The absorption maximum was at 4805 Å. and there was no photographic sensitisation. When the reaction temperature was kept down by cooling with ice, the yield of dye was only 1%.

1-Anilino-5-anilo-1:3-dimethyl-1:3-pentadiene Hydrobromide (V).—A solution of aniline (10 c.c.; 2.2 mols.) and α -lutidine (5 c.c.; 1 mol.) in ether (20 c.c.) was added to a solution of cyanogen bromide

(5 g.; 1 mol.) in ether (10 c.c.), and the mixture warmed for 2 minutes. Hydrobromic acid (14 c.c., d 1.45; 2.5 mols.) was added. The ether-washed solid was obtained in 51% yield (8.08 g.), but tended to become oily on standing in the air. It was used as quickly as possible for dye condensations, being kept meanwhile in a vacuum desiccator.

Bis-2-(3-ethylbenzthiazole)- β -methylheptamethincyanine Iodide (VI).—2-Methylbenzthiazole ethiodide (3.05 g.; 2 mols.) and 1-anilino-5-anilo-1-methyl-1:3-pentadiene hydrobromide (I) (1.72 g.; 1 mol.) were added to ice-cold absolute alcohol (30 c.c.), and a cooled solution of piperidine (1.1 c.c.; 2.2 mols.) in alcohol (5 c.c.) was stirred in. After three days in the ice-chest, the solid was filtered off, washed with alcohol and with ether, and finally with warm water (40 c.c.), after which the yield was 65% (1.84 g.). After recrystallisation from methyl alcohol (650 c.c.), the yield was 33% (0.96 g.) and, after a second recrystallisation (450 c.c. per g.) in the presence of charcoal (0.75 g. per g.), it was 10%. For analysis it was dried to constant weight in a vacuum at 60–80° and this method of drying was applied to the subsequent dyes also (Found: I, 22.6. Calc. for $C_{28}H_{27}N_3IS_2$: I, 22.75%). The green crystals with a golden reflex had m. p. 215° (decomp.) (see B.P. 394,537/1931, example 6).

Bis-2-(3-ethylbenzthiazole)- γ -methylheptamethincyanine Iodide.—A similar preparation was carried out but with (III). The crude product (60% yield) was recrystallised from methyl alcohol (42 c.c. per g.), and gave dark green crystals, in 16% yield (Found: I, 22.8. $C_{27}H_{27}N_3IS_2$ requires I, 22.7%; m. p. 166° (decomp.). The sensitising maximum was at 8150 Å.

Bis-2-(3-ethylbenzthiazole)- δ -methylheptamethincyanine iodide was similarly prepared but with (IV). The crude dye (76% yield) was recrystallised from methyl alcohol (425 c.c. per g.) and gave a 43% yield of light green crystals with a gold reflex (Found: I, 22.8. $C_{28}H_{27}N_3IS_2$ requires I, 22.75%; m. p. 206° (decomp.). Sensitisation extended from 7000 to 9000 Å. with the maximum at 8300.

Bis-2-(3-ethylbenzthiazole)- $\beta\beta'$ -dimethylheptamethincyanine iodide was similarly prepared from 2-methylbenzthiazole ethiodide (2.94 g.) and (II). The product was ground with water (20 c.c.), and twice with acetone (20 c.c. \times 2), boiled out twice with methyl alcohol (50 c.c. \times 2), and recrystallised from methyl alcohol (1350 c.c.), the yield of green crystals then being 10% (0.27 g.) (Found: I, 22.5. $C_{27}H_{29}N_3IS_2$ requires I, 22.2%; m. p. 208° (decomp.). The sensitising maximum was at 8350 Å.

Bis-2-(3-ethylbenzthiazole)- $\beta\delta$ -dimethylheptamethincyanine Iodide.—Starting from 2-methylbenzthiazole ethiodide (12.2 g.) and crude (V), the crude yield was only 2% (0.2 g.). After boiling out with absolute alcohol (5 c.c.) and recrystallisation from methyl alcohol (15 c.c.), it was less than 1% (0.08 g.) [Found (micro-analysis by Weiler and Strauss): I, 22.6. $C_{27}H_{29}N_3IS_2$ requires I, 22.2%]. The bright green crystals had m. p. 155° (decomp.). Photographic sensitisation was from 7200 to 8500 with the maximum at 8200 Å.

Bis-2-(5:6-dimethoxy-3-ethylbenzthiazole)- $\beta\beta'$ -dimethylheptamethincyanine Iodide.—5:6-Dimethoxy-2-methylbenzthiazole ethiodide (5.84 g.; 2 mols.), (II) (2.5 g.; 1 mol.), and absolute alcohol (40 c.c.) were stirred mechanically at 80°. A solution of piperidine (1.8 c.c.; 2.2 mols.) in alcohol (up to 12 c.c.) was added in 12 portions (1 c.c. per minute) and stirring was for 12 minutes. After cooling, the solid was filtered off, washed once with alcohol, twice with warm water (20 c.c. \times 2), and repeatedly with acetone. The residue (0.27 g.; 5% yield) was recrystallised from methyl alcohol (500 c.c.), and the yield was 2% (Found: I, 18.3. $C_{31}H_{37}O_4N_3IS_2$ requires I, 18.3%). The green crystals had m. p. 210° (decomp.).

Bis-2-(3-ethyl-6:7-benzbenzthiazole)- $\beta\beta'$ -dimethylheptamethincyanine Iodide.—This was prepared from 2-methyl-6:7-benzbenzthiazole ethiodide (8.82 g.) and (II), with piperidine in ice-cold alcohol. The washed solid was boiled out with methyl alcohol (100 c.c.) and recrystallised from it (1000 c.c.), being obtained in 8% yield (0.51 g.) (Found: I, 19.2. $C_{28}H_{29}N_3IS_2$ requires I, 18.9%). The bronze crystals had m. p. 187° (decomp.). The sensitising maximum was at 8800 Å. In the corresponding preparation carried out with 2-methyl-4:5-benzbenzthiazole ethiodide, the yield of tricarbocyanine was only 1%.

Bis-2-(3-ethyl-6:7-benzbenzthiazole)- δ -methylheptamethincyanine Iodide.—This was similarly prepared from 2-methyl-6:7-benzbenzthiazole ethiodide (3.55 g.) and (IV). The washed solid (1.02 g.) was boiled out with methyl alcohol (20 c.c.) and recrystallised from it (1100 c.c.). An 18% yield (0.6 g.) was obtained (Found: I, 19.15. Calc. for $C_{28}H_{29}N_3IS_2$: I, 19.3%). The bronze crystals had m. p. 187° (decomp.) (see B.P. 394,537/1931, example 8).

Bis-2-(3-ethylbenzelenazole)- $\beta\beta'$ -dimethylheptamethincyanine Iodide.—2-Methylbenzelenazole ethiodide (5.63 g.) was similarly allowed to react with (II). The washed solid was boiled out with methyl alcohol (70 c.c.), and recrystallised from it (1750 c.c.). The yield (0.97 g.) was 18% (Found: I, 19.3. $C_{27}H_{29}N_3ISe_2$ requires I, 19.4%). The green crystals had m. p. 214–217° (decomp.), the exact temperature depending on the rate of heating. The sensitising maximum was at 8450 Å.

Bis-2-(3-ethylbenzelenazole)- γ -methylheptamethincyanine iodide was similarly prepared from 2-methylbenzelenazole ethiodide (7.71 g.) and (III). The washed product (3.17 g.) was boiled out with methyl alcohol (60 c.c.) and recrystallised from it (1000 c.c.), the yield being 18% (1.26 g.) (Found: I, 19.5. $C_{28}H_{29}N_3ISe_2$ requires I, 19.45%). The green crystals melted at 214° (decomp.). The sensitising maximum was at 8350 Å.

Bis-2-(3-ethylbenzelenazole)- δ -methylheptamethincyanine iodide was similarly prepared from 2-methylbenzelenazole ethiodide (3.52 g.) and (IV). The washed solid (1.65 g.) was boiled out with methyl alcohol (30 c.c.) and recrystallised from it (1400 c.c.), being obtained in 30% yield (0.96 g.) (Found: I, 19.65. $C_{28}H_{29}N_3ISe_2$ requires I, 19.5%). It formed light green crystals with a golden reflex; m. p. 213° (decomp.). Sensitisation was from 7000 to 9000 Å. with a maximum at 8400.

Bis-2-(3-ethyl- Δ^2 -thiazoline)- δ -methylheptamethincyanine Iodide (VII).—This was prepared from 2-methylthiazoline ethiodide (5.14 g.) and (IV). The washed dye (3.85 g.) was recrystallised from methyl alcohol (25 c.c.), and the yield was 59% (2.65 g.) (Found: I, 27.5. $C_{18}H_{21}N_3IS_2$ requires I, 27.45%). It formed bluish-black crystals with a metallic lustre; m. p. 134° (decomp.). Sensitisation was from 6100 to 7500 Å., with the maximum at 7100.

Bis-2-(3-ethyl- Δ^2 -thiazoline)- $\beta\delta$ -dimethylheptamethincyanine Iodide.—In a similar preparation carried out with (V), the yield of washed dye was only 5% and after recrystallisation from methyl alcohol (40 c.c. per g.) was 2% [Found (micro-analysis by Weiler and Strauss): I, 26.8. $C_{19}H_{19}N_3IS_2$ requires

I, 26.65%]. The bluish-grey crystals had m. p. 165° (decomp.). The dye sensitised from 6000 to 7300 with the maximum at 6900 Å.

We are indebted to Miss M. D. Gauntlett for the absorption measurements, and for the sensitising tests to Drs. B. H. Carroll, E. P. Davey, and E. B. Knott.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX.

[Received, October 29th, 1946.]

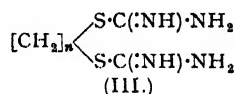
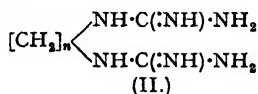
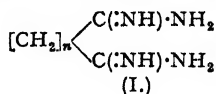
182. Some Alkoxy- and Alkylenedioxydi-amines and Alkoxy- and Alkylenedioxydi-guanidines.

By A. T. FULLER and HAROLD KING.

The aim of the investigation was the preparation of a series of alkoxy- and alkylenedioxydi-amines (*O*-alkyl- and *OO'*-alkylene-hydroxylamines) and the corresponding alkoxy- and alkylenedioxydi-guanidines with a view to their being tested for antiprotozoal and antibacterial activity. Several representatives of all these types have been successfully made, starting from hydroxyurethane. Other methods of approach have been partly successful. Incidentally, two representatives of the hitherto undescribed class of *O*-alkoxydiguanydes have been isolated.*

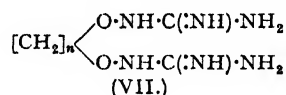
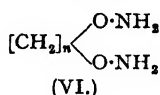
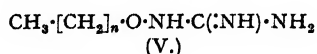
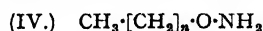
All these substances have been tested on a range of bacteria *in vitro*.

KING, LOURIE, and YORKE (*Lancet*, 1937, ii, 1360; *Ann. Trop. Med. Parasit.*, 1938, 32, 177) discovered that diamidines (I), diguanidines (II), and diisothioureas (III) had a pronounced trypanocidal action, some of the members of the members where $n = 10$ or more being lethal to trypanosomes *in vitro* at a dilution of 1 in 250,000,000



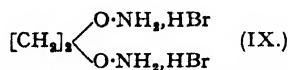
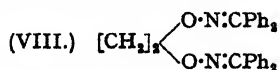
Fuller (*Biochem. J.*, 1942, 36, 548) examined the action of many of these bases, as salts, on a range of bacteria and found that their bacteriostatic titres were lower than their trypanocidal titres, but even so the activity was very pronounced in some of the higher members.

It seemed to us that in further exploration of the parent types the preparation of a series of alkoxyamines (IV), *N*-alkoxyguanidines (V), alkylenedioxydiamines (VI), and alkylenedioxydiguanydes (VII) might be worth undertaking.



Direct alkylation of hydroxylamine leads to *N*-substitution, so for the preparation of *O*-substituted hydroxylamines, the amino-group must be partly or wholly protected. A number of ways of accomplishing this are described in the literature, but without preliminary exploration of these methods it was by no means certain which method would lend itself to the object we had in view.

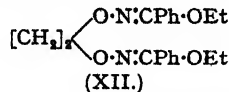
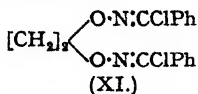
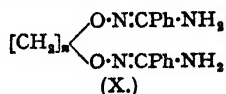
Alkylation of oximes by methyl iodide or methyl sulphate leads, both with the aliphatic ketoximes (Dunstan and Goulding, *J.*, 1901, 79, 628) and with the aromatic ketoximes (Semper and Lichtenstadt, *Ber.*, 1918, 51, 928) to production of *O*- and *N*-methyl ethers. Borek and Clarke (*J. Amer. Chem. Soc.*, 1936, 58, 2020) were, however, able to use acetoxime for the preparation of carboxymethoxyamine, $\text{NH}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ in 60% yield. On these lines a trial was made of the use of benzophenone oxime, which reacted in alcoholic solution with ethylene bromide and sodium ethoxide to give a single homogeneous *ethylenedibenzophenone oxime* of the probable constitution (VIII). The poor yield and slight dubiety about the structure led to the abandonment of this method of approach.



Luxmoore (*J.*, 1895, 67, 1018) claimed to have prepared ethylenedioxydiamine dihydrobromide (IX) by the direct action of ethylene dibromide on hydroxylamine, but Werner and

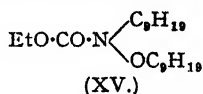
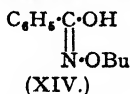
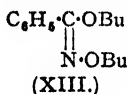
* Curd and Rose (*J.*, 1946, 736) have, however, recently described the preparation of a member of this group of substances.

Gemeseus (*Ber.*, 1896, 29, 1161) pointed out that Luxmoore's claim was inconsistent with the behaviour of hydroxylamine towards alkyl halides. These investigators were, however, able to prepare the corresponding dihydrochloride from the benzamidoxime ethylene ether (X, $n = 2$) of Falck (*Ber.*, 1886, 19, 1481) which, on treatment with nitrite in the presence of hydrochloric acid, gave benzenyl chloride oxime ethylene ether (XI). The latter with sodium ethoxide furnished the ethylene ether of an ethylbenzhydroxamic acid (XII) which, without



characterisation was hydrolysed to ethylenedioxydiamine. As this method seemed applicable to alkylenedioxydiamines, ethylene dibromide, 1:6-dibromohexane, and 1:12-dibromododecane have been condensed with benzamidoxime to give *ethylenedi-OO'-benzamidoxime dihydrochloride*, 1:6-hexamethylenedi-OO'-benzamidoxime (X, $n = 6$), and *dodecamethylenedi-OO'-benzamidoxime* (X, $n = 12$), respectively. In a similar way heptyl bromide was converted into *O-heptylbenzamidoxime* but all attempts to convert the latter or 1:6-hexamethylenedioxybenzamidoxime into the chloride oximes failed completely.

The success of Werner and Gemeseus in obtaining ethylenedioxydiamine, in unstated yield, depended essentially on a method for the preparation of the readily hydrolysable ethylene ether of ethylbenzhydroxamic acid (XII). To explore the possibility of a short route to allied compounds the direct butylation of benzhydroxamic acid was examined. When potassium benzhydroxamate was boiled with butyl bromide in alcohol in presence of potassium carbonate, equal weights of a non-acidic fraction and of an acidic fraction were obtained. The former, on fractional distillation, gave *OO'-dibutyl benzhydroxamate* (XIII) as its main component and



aniline, as a minor component, produced during the reaction by a Lossen rearrangement; (XIII) on hydrolysis with aqueous-alcoholic hydrogen chloride gave mainly ethyl benzoate and butoxyamine hydrochloride.

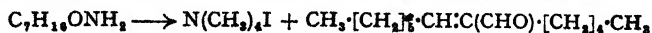
The acidic fraction on distillation proved to be *O'-butyl benzhydroxamate* (XIV) which on hydrolysis with hydrobromic acid gave *butoxyamine hydrobromide* and benzoic acid.

Whilst the foregoing method might prove suitable for the preparation of the alkoxyamines it would clearly lead to complications with alkylene dihalides.

Most of the above methods of approach to the synthesis of *O*-alkyl- and *OO'*-alkylenedioxyhydroxylamines have involved compounds of oxime type where the nitrogen atom is doubly linked to carbon. Lauder W. Jones and his pupils (cf. Jones and Neuffer, *J. Amer. Chem. Soc.*, 1914, 36, 2202) have successfully used hydroxyurethane, $\text{OH} \cdot \text{NH} \cdot \text{CO}_2\text{Et}$ for the preparation of the simplest *O*-alkylhydroxylamines. In our hands this method has proved capable of extension to the higher *O*-alkylhydroxylamines and to the *OO'*-alkylenedioxyhydroxylamines. In the cases of the lower homologues up to heptyl no evidence was found for significant proportions of *N*-alkyl derivatives but from the products of the reaction between nonyl bromide and hydroxyurethane, *nonoxyurethane* and *nonoxynonylurethane* (XV) were obtained by fractional distillation. Similarly, alkylene dibromides have been found to give alkylenedioxydiurethanes except that with trimethylene and tetramethylene dibromides cyclisation took place with production of derivatives of isooxazolidine and tetrahydroisooxazine (King, *J.*, 1942, 432). For the hydrolysis of the urethanes, alkali and acid have been used successfully, but there is always some fission of ammonia.

All the hydroxylamines have been converted into alkoxyguanidines and alkylenedioxydiguanidines by use of *S*-methylisothiurea or cyanamide. Where cyanamide has been employed in excess, two representatives of the hitherto unknown *O*-alkoxydiguanides have been isolated as exemplified by *butoxydiguanide nitrate* and *hexoxydiguanide nitrate*. The former was also prepared by the action of dicyanodiamide on butoxyamine hydrochloride in boiling butyl alcohol. The parent substance hydroxydiguanide also seems to be unknown.

Finally, the complete methylation of heptoxyamine was attempted in methyl alcohol in the presence of potassium carbonate. The products were tetramethylammonium iodide and 2-*n*-heptylidene-*n*-heptaldehyde, identified as its *dinitrophenylhydrazone*:



This reaction is fundamentally the same as that observed by Meisenheimer (*Annalen*, 1913, **397**, 273; cf. Jones and Major, *J. Amer. Chem. Soc.*, 1927, **49**, 1529), who found that evaporation of alcoholic solutions of ethoxy- and propoxy-trimethylammonium hydroxide led to production of acetaldehyde and propaldehyde respectively.

Antibacterial Activity.

The methods used were similar to those previously described (Fuller, *loc. cit.*). The results are summarised in the following table: the figures of inhibitory concentrations are those which prevented visible growth in 20 hours at 37° and are expressed as mg. per 100 c.c. (parts per 100,000). The sign > indicates that the drug was not active at the highest concentration tested.

	In blood.		In broth.			
	<i>Strep. pyogenes.</i>	<i>Strep. pyogenes.</i>	<i>Staph. aureus.</i>	<i>Cl. welchii.</i>	<i>E. coli.</i>	<i>B. proteus.</i>
<i>Alkoxyamines (O-Alkylhydroxylamines).</i>						
CH ₃ -	120	20	75	150	100	300
C ₄ H ₉ -	500	20	100	150	100	500
C ₆ H ₁₃ -	100	5	200	50	200	500
C ₇ H ₁₅ -	200	5	100	50	200	200
C ₈ H ₁₇ -	200	2	10	10	>20	>20
C ₁₀ H ₂₁ -	>5	1	>5	>5	>5	>5
<i>Alkylenedioxydiamines (OO'-Alkylenehydroxylamines).</i>						
-C ₆ H ₁₃ -	50	50	200	100	100	220
-C ₁₀ H ₂₀ -	100	1	100	8	>200	>200
<i>Alkoxyguanidines.</i>						
-C ₄ H ₉ -	100	10	1000	50	1000	>1000
-C ₆ H ₁₃ -	5	5	100	20	100	200
-C ₇ H ₁₅ -	20	2	25	5	50	100
-C ₈ H ₁₇ -	20	1	2	1.5	5	10
-C ₁₂ H ₂₅ -	>10	0.2	0.8	1	2	5
<i>Alkylenedioxydiguanidines.</i>						
-C ₆ H ₁₃ -	50	10	200	200	>1000	>1000
-C ₁₀ H ₂₀ -	20	0.8	10	2	20	100

As is usual with basic drugs, these drugs are more active against the Gram-positive than the Gram-negative bacteria (*E. coli* and *B. proteus*). In a homologous series it is usual for activity to increase with chain length up to a point above which the activity decreases. The alkoxyguanidines, which are stronger bases than the *O*-alkylhydroxylamines, do not appear to have reached their maximum activity at C₁₂, while the *O*-alkylhydroxylamines show signs of having done so. This power of a more strongly basic group to support activity in a longer chain has been noted before (Fuller, *ibid.*).

The basicity of the compounds increases with the chain length. They are, however, such weak bases (the pH of their salts varies from pH 3 to pH 5.5) that none would be appreciably ionized at pH 7.5, so the observed differences of activity are probably not due to differences in their degrees of ionization.

The *O*-alkylhydroxylamines turned the colour of blood to brown or black, but the change was less marked with the alkoxyguanidines. Blood greatly reduced the activity of the drugs with increasing effect as the series was ascended, until the higher members retained 1% or less of the activity shown in broth.

EXPERIMENTAL.

Hydroxyurethane.—Hydroxylamine hydrochloride (27.8 g.; 1 mol.) was added to a solution of anhydrous sodium carbonate (62.4 g.; 1.5 mols.) in water (184 c.c.). The vigorously stirred solution, with salt in suspension, was slowly treated with ethyl chloroformate (42.4 g.), the temperature being kept approximately at that of the room. The final solution was acidified and extracted with ether in a continuous extractor. The yield of hydroxyurethane, dried over sodium sulphate, was about 94%. This method is based on Hantzsch's process (*Ber.*, 1894, **27**, 1255) and is more convenient than that of Jones (*Amer. Chem. J.*, 1898, **20**, 39).

Butoxyurethane and Butoxyamine Hydrochloride.—Hydroxyurethane (10.5 g.) and butyl iodide (18.4 g.) were added to ethyl alcohol (30 c.c.) containing dissolved potassium hydroxide (6.6 g., 85% pure) and the mixture boiled for 5 hours. The alcohol was removed, and the crude butoxyurethane recovered by ether extraction; yield 11.65 g. This urethane was boiled for one hour with potassium hydroxide (16.2 g.; 4 mols.) in water (32.4 c.c.). A solid potassium salt separated first but this quickly

disappeared and was followed by separation of an oily layer. The latter was taken up in ether, and the ethereal extract treated with slight excess of 3*N*-hydrochloric acid. This acid solution was evaporated to dryness, and the crystalline residue dissolved in boiling ethyl acetate. Butoxyamine hydrochloride, *m. p.* 156–157°, separated in glistening leaflets (5.3 g.) identical with the product obtained from the butylation of benzhydroxamic acid (see below).

Butoxyguanidine Nitrate.—Butoxyamine hydrochloride (9.3 g.) and cyanamide (6.3 g.) were boiled in absolute alcohol (50 c.c.) for six hours. The alcohol was removed, water added, and the required nitrate (9.8 g.) precipitated by adding excess of solid ammonium nitrate. It was twice crystallised from 1.5 vols. of water and separated in well-formed tablets, *m. p.* 77–78° (Found: C, 31.1; H, 7.5. $C_8H_{15}ON_3.HNO_3$ requires C, 30.9; H, 7.3%). On fractionation of the mother-liquors a by-product was obtained in small quantity which separated from water in nodules but from alcohol in clusters of feathery needles, *m. p.* 116–117°. This proved to be *butoxydiguanide nitrate* (Found: C, 30.9; H, 6.3; N, 34.8. $C_8H_{15}ON_6.HNO_3$ requires C, 30.5; H, 6.8; N, 35.6%). A specimen was synthesised for comparison by boiling butoxyamine hydrochloride and dicyanodiamide in butyl-alcoholic solution and conversion into the nitrate. On admixture of the above by-product with this substance there was no depression of *m. p.*

Hexoxyurethane.—Potassium hydroxide (16.8 g.) in boiling absolute alcohol (168 c.c.) was treated with a mixture of hydroxyurethane (31.5 g.) and hexyl bromide (49.5 g.), and the resulting solution boiled for 6 hours. After removal of potassium bromide by filtration the alcohol was distilled off, the residue dissolved in water, and the *hexoxyurethane* extracted by ether and fractionally distilled; *b. p.* 147–148°/16 mm.; yield 36.6 g. (Found: N, 7.3. $C_8H_{19}O_3N$ requires N, 7.4%).

Acid hydrolysis. The foregoing urethane (18 g.) was boiled for two hours with constant-boiling hydrobromic acid solution (40 c.c.). On cooling, an oily layer separated which soon crystallised. It was collected, well pressed, and then washed with a little light petroleum to remove an oil; yield 7.9 g. On crystallisation of the dried solid from ethyl acetate, *hexoxyamine hydrobromide* separated in pearly flakes, *m. p.* 141° (Found: C, 36.7; H, 8.2. $C_8H_{15}ON.HBr$ requires C, 36.4; H, 8.2%). The hydrobromic acid mother-liquor after extraction with ether to remove non-basic material, mainly hexyl bromide, was basified and again extracted with ether. In this way a small quantity (2 g.) of the base was obtained, *b. p.* 159°/750 mm. (Found: C, 61.7; H, 13.0; N, 11.9. $C_8H_{15}ON$ requires C, 61.5; H, 12.8; N, 12.0%).

Alkaline hydrolysis. The urethane (36.4 g.) was boiled with potassium hydroxide (43 g.; 4 mols.) in water (215 c.c.) for 3.5 hours. The oily layer was taken up in ether, and the ethereal extracts combined and extracted with 2*N*-hydrochloric acid (150 c.c.). The acid extract was evaporated to dryness with absolute alcohol, dissolved in a small volume of dry ethyl acetate, and kept at 0°.

Hexoxyamine hydrochloride separated in pearly scales, and a further quantity was obtained from the mother-liquor by addition of dry ether, total yield 20.4 g. The ethereal extract (above) was evaporated and gave unchanged urethane (5.8 g.). The hydrochloride is sparingly soluble in boiling ethyl acetate and melts at 150–151° (Found: C, 46.9; H, 10.6. $C_8H_{15}ON.HCl$ requires C, 46.9; H, 10.5%).

Hexoxyguanidine Nitrate.—(1) *From methylisothiouraea.* Hexoxyamine (3.5 g.; 1 mol.) in alcohol (20 c.c.) was treated with methylisothiouraea sulphate (4.2 g.), and the solution boiled gently for 1 hour and then evaporated to a small volume; on keeping, it deposited methylisothiouraea sulphate (0.7 g.). The residue obtained on evaporation to dryness was dissolved in water, and excess of ammonium nitrate added. Crude *hexoxyguanidine nitrate* (4.7 g.) gradually crystallised. It separated from water on recrystallisation in tablets, *m. p.* 72–73° (Found: C, 38.2; H, 8.5; N, 24.8. $C_7H_{11}ON_3.HNO_3$ requires C, 37.8; H, 8.2; N, 25.2%).

(2) *From cyanamide.* Hexoxyamine hydrochloride (7.68 g.) and cyanamide (4.4 g.; 2 mols.) were boiled in alcohol (25 c.c.) for 6 hours. The solvent was removed, water added, and then excess of ammonium nitrate. The oil which separated gradually solidified and after a tedious fractional crystallisation from water gave *hexoxyguanidine nitrate* (4.1 g.), identical with the above, and *hexoxydiguanide nitrate* (0.6 g.), *m. p.* 115–116°, which separated from water or alcohol in tiny plates (Found: C, 36.8; H, 7.5; N, 31.8. $C_8H_{15}ON_6.HNO_3$ requires C, 36.3; H, 7.6; N, 31.8%).

O-Hexylcholestenone Oxime.—Equimolecular quantities (*M*/1000) of cholestenone and hexoxyamine were boiled in ethyl alcohol (5 c.c.) for an hour. The crystalline *oxime* which separated was recrystallised three times from ethyl alcohol and separated in plates, *m. p.* 70° (Found: C, 81.4; H, 11.8. $C_{33}H_{51}ON$ requires C, 81.9; H, 11.9%).

In a similar way *O-hexylcholestanone oxime*, *m. p.* 51°, was obtained, crystallising in flattened prisms from alcohol (Found: C, 81.9; H, 12.2. $C_{33}H_{53}ON$ requires C, 81.6; H, 12.3%).

Heptoxyurethane.—This was prepared in the same way as the lower homologue, the yield of product, *b. p.* 158°/20 mm., being 47% (Found: N, 6.8, 6.9. $C_{10}H_{21}O_3N$ requires N, 7.0%).

Heptoxyamine Hydrobromide.—This salt was prepared by acid hydrolysis as described for its lower homologue, the yield of *hydrobromide*, *m. p.* 142°, from 38.4 g. of heptoxyurethane being 34.5 g. On crystallisation from ethyl acetate it separated in plates, *m. p.* 143° (Found: C, 39.7; H, 8.8. $C_9H_{17}ON.HBr$ requires C, 39.6; H, 8.6%). The hydrobromic acid mother-liquors on extraction with ether gave heptyl bromide (1.8 g.), *b. p.* 170–180°/749 mm.; and after the mother-liquors had been made alkaline, ether extraction gave *O-heptoxyamine*, 0.9 g. This base was prepared in larger quantity from its salt and had *b. p.* 179°/761 mm. (Found: C, 64.7; H, 13.2. $C_9H_{17}ON$ requires C, 64.1; H, 13.1%).

Methylation of Heptoxyamine.—The amine (1.31 g.) and methyl iodide (3.1 c.c.) in methyl alcohol (25 c.c.) were boiled with anhydrous potassium carbonate (4.1 g.) for 3 hours. The solvent was removed, the residue treated with a little water and ether and filtered from some well-formed prisms (0.7 g.), which were crystallised from methyl alcohol (90 c.c.) and were unmelted at 360°. This substance proved to be tetramethylammonium iodide (picrate, *m. p.* 312° undepressed by an authentic specimen).

The ethereal extract of the aqueous liquor on distillation left an oil with a strong sweet odour with the reactions of an aldehyde. It readily gave a *dinitrophenylhydrazone*, red needles (0.1 g.), *m. p.* 129°, from alcohol. This on analysis proved to be derived from 2-*n*-heptylidene-*n*-heptaldehyde (Found: C, 61.6; H, 7.8; N, 14.5. $C_{20}H_{38}O_2N_4$ requires C, 61.5; H, 7.8; N, 14.4%).

Heptoxyguanine Nitrate.—This salt was prepared in a similar way to the lower homologue, the yield of crude nitrate from 3.9 g. of heptoxamine being 4 g. It crystallised from water in prisms, m. p. 72° (Found: C, 41.6; H, 8.6; N, 24.1. $C_7H_{15}ON_3 \cdot HNO_3$ requires C, 40.7; H, 8.5; N, 23.7%).

Heptoxy-3:5-dinitrobenzamide.—Heptoxamine (1.31 g.) in pyridine (5 c.c.) was heated with 3:5-dinitrobenzoyl chloride (1 mol.) at 100° for 30 minutes. On cooling and adding excess of hydrochloric acid, the product crystallised (2.6 g.). It was purified by grinding with sodium bicarbonate solution and could then be crystallised from ether as pale yellow needles, m. p. 83–84° (Found: C, 52.1, 52.1; H, 6.0, 5.9; N, 12.7. $C_{14}H_{15}O_5N_5$ requires C, 51.7; H, 5.8; N, 12.9%).

Nonoxyurethane.—The crude alkylated urethane prepared in the usual manner from hydroxyurethane (8.4 g.) and nonyl bromide (16.5 g.) was fractionally distilled and gave **nonoxyurethane** (8.4 g.), b. p. 179°/20 mm. (Found: N, 6.1. $C_{11}H_{23}O_2N$ requires N, 6.1%), and a higher-boiling fraction of **nonoxynonylurethane** (3.0 g.), b. p. 189°/2 mm. (Found: N, 3.9. $C_{21}H_{43}O_2N$ requires N, 3.9%).

Nonoxamine Hydrobromide.—The urethane (8.4 g.) was boiled with constant-boiling hydrobromic acid (25 c.c.) for 2 hours. On cooling, the oily layer which separated gradually crystallised. It was collected, washed with a little 48% hydrobromic acid, and finally with a few drops of ether; yield 5.3 g. It was crystallised from ethyl acetate (20 c.c.) and separated in flakes, m. p. 138°; yield 4.1 g. (Found: C, 44.2; H, 9.4. $C_9H_{21}ON \cdot HBr$ requires C, 44.9; H, 9.2%). The hydrobromic acid mother-liquor on extraction with ether gave nonyl bromide (3.0 g.), b. p. 215–220°/756 mm.

Nonoxamine Hydrochloride.—The urethane (33.2 g.) was boiled with 16% hydrochloric acid (100 c.c.) for 24 hours. The hydrochloride separated in needles (10.6 g.), m. p. 146–149° (Found: C, 55.2; H, 11.3; Cl, 18.4. $C_9H_{21}ON \cdot HCl$ requires C, 55.6; H, 11.5; Cl, 18.2%).

Nonoxyguanine Nitrate.—Nonoxamine hydrochloride (3.9 g.) was dissolved in *n*-sodium hydroxide (20 c.c.) and methylisothiouraea sulphate (2.78 g.) in alcohol (15 c.c.) added. After boiling gently for 1 hour, the solution was evaporated to dryness, the residue dissolved in absolute alcohol, and the sodium chloride removed. The solution was again evaporated to dryness, the residue dissolved in water, and ammonium nitrate added in excess. The nitrate was collected (4.8 g.) and crystallised from water, separating in needles, m. p. 61–62° (Found: N, 20.9. $C_{10}H_{22}ON_3 \cdot HNO_3$ requires N, 21.2%).

Dodecoxyurethane.—From lauryl bromide (37 g.) the crude urethane (39.0 g.) was obtained in the usual way. As it could not be distilled without some decomposition, it was hydrolysed without further purification.

Dodecoxyamine Hydrobromide.—The urethane (20 g.) was boiled with constant-boiling hydrobromic acid (40 c.c.) for 3 hours; on cooling, the oily upper layer crystallised. It was collected by filtration, well pressed, and then washed with ether to remove adhering oil. The hydrobromide (9.1 g.) was recrystallised from ethyl acetate, separating in pearly plates, m. p. 133° (Found: C, 51.0; H, 9.9. $C_{12}H_{25}ON \cdot HBr$ requires C, 51.0; H, 10.0%). The hydrobromic acid filtrate was extracted with ether, and the extract on fractional distillation gave lauryl bromide (9.9 g.), b. p. 138–144°/18 mm.

Dodecoxyguanine Nitrate.—The preceding hydrobromide (5.64 g.) was dissolved in *n*-sodium hydroxide solution (20 c.c.) and methylisothiouraea sulphate (2.78 g.) in alcohol (15 c.c.) added. The reaction mixture was worked up as described for the corresponding nonyl derivative. The yield of crude nitrate was 4.1 g., and on crystallisation from water (100 c.c.) it separated in leaflets, m. p. 79° (Found: C, 50.9; H, 9.6; N, 18.0. $C_{13}H_{27}ON_3 \cdot HNO_3$ requires C, 50.9; H, 9.9; N, 18.3%).

1:6-Hexamethylenedioxydiurethane.—Hexamethylene dibromide (24.4 g.), hydroxyurethane (21 g.), and potassium hydroxide (11.2 g.) were boiled together in absolute alcohol (100 c.c.) for 6 hours. The alcohol was removed and an ethereal extract made of the residue when diluted by water. Removal of the ether left the crude urethane (28.7 g.), which could not be distilled at 1 mm. without decomposition.

1:6-Hexamethylenedioxydiamine Dihydrochloride.—The preceding urethane was boiled for 2.5 hours with potassium hydroxide (40 g.) in water (80 c.c.), during which period there was some evolution of ammonia. The oily layer was taken up in ether and distilled, the fraction, b. p. 90–120°/1 mm. (9.8 g.), being collected and redistilled, b. p. 112°/1 mm. (7.5 g.). It was treated with the calculated amount of *n*-hydrochloric acid, and the dihydrochloride was recrystallised twice from spirit. It separated in tiny leaflets, m. p. 220° (Found: C, 32.7; H, 8.1. $C_6H_{16}O_2N_2 \cdot 2HCl$ requires C, 32.6; H, 8.2%).

Attempts to hydrolyse the urethane with constant-boiling hydrobromic acid or 16% hydrochloric acid gave very poor yields of base. For instance, the diurethane (14 g.) was boiled for 1.5 hours with 16% hydrochloric acid (50 c.c.) and gave a basic fraction (0.7 g.). A portion of this was converted into the *dipicrolonate* by mixing the calculated amounts of the components in alcohol. It was very sparingly soluble in boiling absolute alcohol and crystallised in minute needles, m. p. 229° (Found: C, 45.9; H, 4.7. $C_6H_{14}O_2N_2 \cdot 2C_{10}H_7O_2N_2$ requires C, 46.4; H, 4.8%).

1:6-Hexamethylenedioxydiguanidine Dinitrate.—The preceding dihydrochloride (2.21 g.) was boiled in alcohol (20 c.c.) with cyanamide (1.68 g.) for 6 hours. The solvent was removed, and a small volume of water added, followed by excess of ammonium nitrate. An oil separated which eventually crystallised. It was collected, dried, and recrystallised from absolute alcohol or water, separating in pointed prisms, m. p. 123° (efferv.). The behaviour of the solid on heating in a capillary is variable: no melting takes place and the point of effervescence may occur at any temperature between 121° and 125° (Found: C, 27.2; H, 5.9; N, 30.7. $C_6H_{20}O_4N_6 \cdot 2HNO_3$ requires C, 26.8; H, 6.2; N, 31.3%).

1:10-Decamethylenedioxydiurethane.—Dibromodecane (15 g.) and hydroxyurethane (10.5 g.) were boiled in absolute alcohol (60 c.c.) containing potassium hydroxide (5.6 g.) for 6 hours. The alcohol was removed by distillation and replaced by water, and the diurethane extracted with ether. On removal of the ether, the residue (15.9 g.) crystallised on cooling to 0°. A portion was crystallised from ether–light petroleum and gave the urethane, m. p. 53–55° (Found: C, 55.6; H, 9.3. $C_{14}H_{30}O_2N_2$ requires C, 55.1; H, 9.3%). Attempts to hydrolyse the main bulk of diurethane by acid were unsuccessful.

1:10-Decamethylenedioxydiamine Dihydrochloride.—The crude urethane from 15.0 g. of dibromodecane was boiled for 1 hour with potassium hydroxide (20.2 g.) in water (40.6 c.c.). A potassium salt separated at first but was soon replaced by an oily layer. During the hydrolysis some ammonia was given off. The oil was taken up in ether, the ether removed, and the residue distilled; yield 3.9 g.,

b. p. 144—145°/1 mm. The undistilled residue could be again hydrolysed to give a further quantity of base. The pure distilled base which readily solidified was converted into the *dihydrochloride* which could be crystallised from alcohol but preferably from 3*N*-hydrochloric acid, separating in tiny needles, m. p. 220° (Found: C, 43.1; H, 9.2. $C_{10}H_{14}O_2N_2 \cdot 2HCl$ requires C, 43.3; H, 9.4%).

1:10-Decamethylenedioxydiguanylidine Dinitrate.—The preceding dihydrochloride (1.4 g.) was boiled in alcoholic solution (10 c.c.) with cyanamide (0.84 g.) for 6 hours. The alcohol was removed, and the residue dissolved in water and treated with ammonium nitrate. The required *dinitrate* (2.2 g.) readily separated as a crystalline solid which was recrystallised from spirit (5 c.c.) and separated in rosettes of compact crystals, m. p. 135° (efferv.). The point of effervescence, like that observed for the corresponding hexamethylene derivative, is very variable, values as high as 147° being observed (Found: C, 35.1; H, 7.2; N, 26.5. $C_{12}H_{18}O_2N_6 \cdot 2HNO_3$ requires C, 34.8; H, 7.3; N, 27.0%).

Butylation of Benzhydroxamic Acid.—Potassium benzhydroxamate (46.7 g.), spirit (225 c.c.), butyl bromide (41.1 g.), and excess of potassium carbonate were boiled for 15 hours, the alcohol removed by distillation, and the residue diluted with water and ether and filtered from unchanged potassium benzhydroxamate (5.6 g.). The combined ethereal extracts were treated with 7 successive portions of 2*N*-sodium hydroxide (98 c.c. in all) to remove acidic substances. The residual ethereal solution on evaporation left non-acidic substances (A, 23.6 g.). The alkaline extract on acidification and extraction with ether gave an acidic fraction (B, 23.9 g.).

Fraction (A), on fractional distillation, gave aniline (3.0 g.) and a main fraction (16.2 g.), b. p. 175—180°/13 mm., which on redistillation gave *O*-*dibutyl benzhydroxamate*, b. p. 175—180°/13 mm. (Found: C, 72.2; N, 9.1; N, 5.5. $C_{18}H_{25}O_2N$ requires C, 72.3; H, 9.2; N, 5.6%). The dibutyl derivative was boiled with a mixture of absolute alcohol (100 c.c.) and hydrochloric acid (25 c.c., *d* 1.16) for 4 hours. The resultant solution was diluted with 2 vols. of water and extracted with ether. Washing of the latter with aqueous sodium bicarbonate removed benzoic acid (0.72 g.), and fractional distillation gave ethyl benzoate (8.35 g.), b. p. 213°, with no higher fraction. The main hydrochloric acid mother-liquor was evaporated to dryness under reduced pressure, finally with alcohol, and a small crop of ammonium chloride removed. On re-evaporation to dryness and solution in dry ether, butoxyamine hydrochloride separated as leaflets, m. p. 154°, undepressed by an authentic specimen (Found: Cl, 28.6. Calc.: Cl, 28.2%).

The acidic fraction (B), on distillation at 15 mm., had b. p. 182° and was much more viscous than the dibutyl compound; yield 17.0 g. Analysis showed it to be *O*-*butyl benzhydroxamate* (Found: C, 68.1; H, 8.0; N, 7.6. $C_{11}H_{15}O_2N$ requires C, 68.4; H, 7.8; N, 7.2%). It was hydrolysed by boiling with constant-boiling hydrobromic acid for 6.5 hours. The solution was diluted with an equal volume of water, and ether extraction removed benzoic acid in quantitative yield. The hydrobromic acid solution was evaporated to small volume under reduced pressure with two additions of water, and the *butoxyamine hydrobromide* (4.8 g.) collected. It was crystallised from ethyl acetate and separated in pearly leaflets, m. p. 159—160° (Found: Br, 47.2. $C_4H_{11}ON \cdot HBr$ requires Br, 47.0%). It was converted in aqueous solution by treatment with silver chloride into butoxyamine hydrochloride which, unlike the hydrobromide, is very sparingly soluble in boiling ethyl acetate. It crystallised in pearly leaflets, m. p. 156—157° (Found: Cl, 28.4. Calc.: Cl, 28.2%). Neuffer and Hoffman (*J. Amer. Chem. Soc.*, 1925, 47, 1686) gave m. p. 152—153°.

O-Heptylbenzamidoxime.—Sodium (9.2 g.) was dissolved in absolute alcohol (150 c.c.) and, after addition of benzamidoxime hydrobromide (43.4 g.) and heptyl bromide (35.8 g.), was boiled for 6 hours. The alcohol was removed, and the residue treated with water and ether. The ethereal extract on distillation left a crystalline solid (42.7 g.) which distilled at 192°/11 mm. *O*-Heptylbenzamidoxime crystallised from ether in needles, m. p. 40—50° (Found: C, 71.9; H, 9.5. $C_{11}H_{21}ON$ requires C, 71.6; H, 9.5%). Attempts to convert this amidoxime into benzenyl chloride oxime *O*-heptyl ether by the action of nitrite in hydrochloric acid solution were unsuccessful. The amidoxime forms a sparingly soluble, oily hydrochloride which is not attacked by the nitrite, and an attempt to circumvent this by carrying out the reaction in glacial acetic acid with amyl nitrite and hydrochloric acid was also unsuccessful.

Ethylenedi-*O*-benzamidoxime Dihydrochloride.—Ethylene bromide (4.7 g.), benzamidoxime (6.8 g.), and absolute alcohol (20 c.c.), which had reacted with sodium, 1.2 g.) were boiled together for 4 hours. The alcohol was removed by distillation, and the residue dissolved in water and made alkaline by addition of excess of 2*N*-sodium hydroxide solution. The solid which separated was dissolved in 3*N*-hydrochloric acid and readily crystallised in needles; yield 1.1 g., m. p. 234—235° (Found: C, 51.8; H, 5.7. $C_{12}H_{18}O_2N_4 \cdot 2HCl$ requires C, 51.7; H, 5.4%). The hydrochloric acid mother-liquor on basification gave a further 0.25 g., m. p. 161°, of ethylenedibenzamidoxime base. No yields for this reaction are quoted by Falck (*Ber.*, 1886, 19, 1485) or by Werner and Gemseus (*ibid.*, 1896, 29, 1162).

1:6-Hexamethylenedi-*O*-benzamidoxime.—Sodium (4.6 g.) was dissolved in absolute alcohol (100 c.c.), and benzamidoxime hydrobromide (21.7 g.), dissolved in warm absolute alcohol (20 c.c.), was added; a sodium salt separated. Hexamethylene bromide (12.15 g.) was then added, and the solution boiled for 6 hours. The alcohol was removed, and the residue treated with water. *Hexamethylenedi-benzamidoxime* separated as an oil which soon solidified (14.7 g.). When crystallised from 70% alcohol and then from absolute alcohol it had m. p. 106° (Found: C, 67.2; H, 7.6; N, 15.5. $C_{20}H_{28}O_2N_4$ requires C, 67.7; H, 7.4; N, 15.8%). Attempts to convert this substance into hexamethylenedi-*O*-benzenyl chloride oxime were not successful.

1:12-Dodecamethylenedi-*O*-benzamidoxime.—Sodium (8.2 g.) was dissolved in absolute alcohol (250 c.c.), and benzamidoxime (21.7 g.) and dodecamethylene bromide (16.35 g.) added. The solution was boiled for 4 hours, the alcohol removed by distillation, and the residue made alkaline with *N*-sodium hydroxide solution. The oil which separated rapidly crystallised; yield 18 g. The crude *oxime* was very soluble in methyl alcohol but could best be crystallised from this solvent. It separated in broad short needles, m. p. 105—106° (Found: C, 71.4; H, 8.6. $C_{22}H_{30}O_2N_4$ requires C, 71.2; H, 8.7%). With 3*N*-hydrochloric acid it forms an oily hydrochloride.

Ethylenedi-*O*-benzophenone Oxime.—Benzophenone oxime (9.85 g.) and ethylene bromide (4.7 g.) were added to sodium ethoxide solution prepared from absolute alcohol (25 c.c.) and sodium (1.15 g.).

On boiling, sodium bromide rapidly separated; heating was continued for 6 hours. When cold, the sodium bromide and admixed needles were collected and the former removed by water, leaving the oxime (1.7 g.), which crystallised from absolute alcohol (60 c.c.) in pearly leaflets, m. p. 123–124° (Found: C, 80.3; H, 5.4; N, 6.4. $C_{16}H_{18}O_4N_2$ requires C, 80.0; H, 5.6; N, 6.7%). There was no evidence for the presence of any isomeric ether, the alcoholic mother-liquors giving only unchanged benzophenone oxime.

Preparation of Benzamidoxime Hydrobromide. Isolation of 2:4-Diphenyl-1:3:5-oxadiazole.—Phenyl cyanide (103 g.), hydroxylamine hydrochloride (69.5 g.), and anhydrous sodium carbonate (53 g.) were treated with water (150 c.c.), and ethyl alcohol added until the solution was homogeneous. The solution was boiled for 18 hours, the alcohol removed by distillation, and the aqueous residue extracted with ether. The ethereal extract was shaken with 24% aqueous hydrobromic acid (400 c.c.), and the latter on concentration gave a 76% yield of *benzamidoxime hydrobromide*, crystallising in prisms, m. p. 183° (Found: C, 39.0; H, 4.7. $C_7H_8ON_2 \cdot HBr$ requires C, 38.7; H, 4.2%). The ethereal solution on fractional distillation gave phenyl cyanide (9.5 g.) and a non-volatile crystalline residue (2.35 g.). The latter on crystallisation from methyl alcohol separated in long silky needles, m. p. 107°, which proved to be 2:4-diphenyl-1:3:5-oxadiazole (Found: C, 75.4; H, 4.8. Calc. for $C_{14}H_{10}ON_2$: C, 75.7; H, 4.5%). The final hydrobromic acid mother-liquor contained benzamide (4.0 g.).

Wolf (*Ber.*, 1898, **31**, 2111) gives m. p. 168° for benzamidoxime hydrochloride. In our hands this salt crystallised from alcohol and ether in stout prisms, m. p. 203° (Found: C, 48.9; H, 5.3; Cl, 20.5. Calc. for $C_7H_8ON_2 \cdot HCl$: C, 48.7; H, 5.3; Cl, 20.5%).

Our thanks are due to Mr. E. V. Wright for able assistance in the experimental work.

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[Received, October 18th, 1946.]

183. 3-Deoxy-1-xylose.

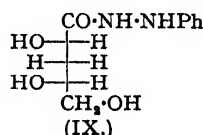
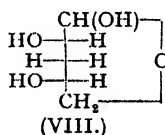
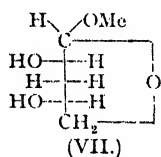
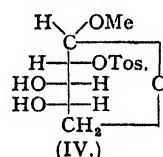
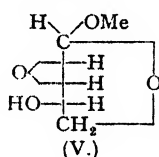
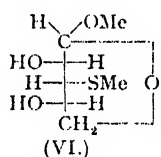
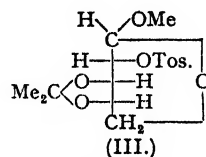
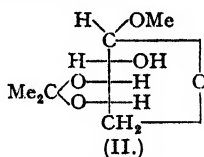
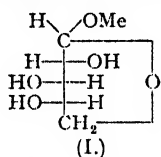
By S. MUKHERJEE and A. R. TODD.

In the course of experiments initiated in search of new synthetic routes to 2-deoxyribose derivatives, 2:3-anhydro- β -methyl-1-ribofuranoside, prepared from β -methyl-1-arabopyranoside, has been treated with sodium thiomethoxide and the product refluxed in alcohol with Raney nickel. The product was 3-deoxy- β -methyl-1-xylopyranoside containing at most only traces of a 2-deoxypentoside. Acid hydrolysis gave 3-deoxy-1-xylose as a syrup, characterised as its *p*-nitrophenylosazone, and yielding on oxidation *l*-erythro-1:3:4-trihydroxyvaleric acid isolated as its phenylhydrazide. Hydrogenolysis of the same anhydro-glycoside gave mainly 3-deoxy- β -methyl-1-xylopyranoside, apparently accompanied by a small amount of a 2-deoxypentoside, since the product showed a small uptake of oxidant on titration with periodate. 2:3-Anhydro- α -methyl-1-ribofuranoside treated in similar fashion with sodium thiomethoxide, followed by refluxing in alcohol with Raney nickel, also gave a product whose major constituent was 3-deoxy- α -methyl-1-xylopyranoside, since the syrupy sugar obtained from it by hydrolysis yielded 3-deoxy-1-xylose *p*-nitrophenylosazone on warming with *p*-nitrophenylhydrazine.

THE work described in this paper was undertaken in connection with studies on the synthesis of purine and pyrimidine nucleosides in progress in this laboratory, and which required for extension to the deoxyribonucleosides considerable quantities of 2-deoxy-*D*-ribose. 2-Deoxy-*L*-ribose has been prepared from *L*-arabinose (Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803; Levene, Mikeska, and Mori, *ibid.*, 1930, **85**, 785) using the standard glycol route first developed by Fischer (*Ber.*, 1914, **47**, 196), but the exploration of other routes which might give better yields of 2-deoxyribose derivatives seemed desirable. The use of 2:3-anhydro-sugar derivatives as intermediates in the synthesis of deoxy-hexoses has recently been described by Prins, Reichstein, and their co-workers who have prepared in this way various derivatives of 3-deoxy-*D*-glucose (Prins, *Helv. Chim. Acta*, 1946, **29**, 1), 2-deoxy-*D*-allose (Jeanloz, Prins, and Reichstein, *ibid.*, p. 371), cymarose (Prins, *ibid.*, p. 378) and 3-deoxy-*L*-mannose (Bollinger and Prins, *ibid.*, p. 1061). Following a discussion with the Swiss workers it was agreed that we should seek to apply similar methods in the pentose series in the hope that they would lead to a preparative method for 2-deoxyribose derivatives. For convenience we first carried out the proposed sequence of reactions starting with *L*-arabinose, which was expected to yield finally either 2-deoxy-*L*-ribose or 3-deoxy-1-xylose or possibly a mixture of both. In fact, it was found that 3-deoxy-1-xylose was formed as the main product; no 2-deoxy-*L*-ribose derivative could be isolated, although there was some evidence that traces of 2-deoxy-derivatives were formed.

β -Methyl-1-arabopyranoside (I) condensed with acetone to give an acetone derivative whose formulation as 3:4-isopropylidene β -methyl-1-arabopyranoside (II) follows from the transformations described below. Treatment of (II) with *p*-toluenesulphonyl chloride in pyridine yielded 2-*p*-tosyl 3:4-isopropylidene β -methyl-1-arabopyranoside (III) hydrolysed to 2-*p*-tosyl β -methyl-1-arabopyranoside (IV). The location of the tosyl group in (IV), and hence the structures

allotted to (II) and (III), are confirmed by the fact that on titration of (IV) with periodate 1 mol. of oxidant is consumed. Cold methanolic sodium methoxide converted (IV) into a crystalline anhydro-compound formulated from its mode of preparation as 2:3-*anhydro*- β -methyl-1-ribofuranoside (V) which, warmed with methanolic sodium thiomethoxide, yielded a syrupy sulphur-containing glycoside. Assuming a *trans*-opening of the ethylene oxide ring of (V) with inversion at the carbon atom to which the sulphur attaches itself this product might have been 3-methylthio β -methyl-1-xylopyranoside (VI), 2-methylthio β -methyl-1-arabopyranoside, or a mixture of both. Although from the experience of Jeanloz, Prins, and Reichstein (*loc. cit.*) in the *d*-allose series production of the 2-methylthio-product in reasonable amount might have been expected, subsequent reactions show that our product consisted almost entirely of (VI), the 2-methylthio-compound being present at most in traces. The syrupy methylthio-compound was refluxed in alcoholic solution with Raney nickel, prepared according to Mozingo *et al.* (*J. Amer. Chem. Soc.*, 1943, 65, 1013); it then yielded a sulphur-free glycoside which was stable to periodate, the uptake of oxidant on titration being within the limits of experimental error. This product we regard as 3-deoxy- β -methyl-1-xylopyranoside (VII). The possibility that it was contaminated by a trace of 2-deoxy- β -methyl-1-ribose cannot be excluded since it could not be crystallised and it gave a feeble green colouration in the Keller-Kiliani test commonly regarded as specific for 2-deoxy-sugars. Acid hydrolysis of (VII) yielded the free 3-deoxy-1-xylose (VIII) as a syrup yielding a crystalline *p*-nitrophenylosazone. The structure allotted to (VIII) was confirmed by oxidation with bromine water, lactonisation of the acid produced, and conversion into a crystalline phenylhydrazide, which agreed in m. p., analysis, and, within the limits of error, optical rotation with *l*(+)-*erythro*-1:3:4-trihydroxyvaleric acid phenylhydrazide (IX) prepared by Nef (*Annalen*, 1910, 376, 48), who on the basis of its dextrorotation described it as the *d*-*erythro*-compound.



As an alternative route the ethylene oxide ring in (V) was opened by hydrogenolysis under pressure using a nickel catalyst. The syrupy product produced was again mainly (VII) but there was more evidence of the presence of an appreciable amount of a 2-deoxy-pentose derivative, since the green colour produced in the Keller-Kiliani test, although weak, was stronger than in the case of the product obtained *via* the methylthio-glycoside, and on periodate titration 0.17 mol. of oxidant was consumed. On acid hydrolysis followed by treatment of the syrupy free sugar with *p*-nitrophenylhydrazine, however, only the *p*-nitrophenylosazone of 3-deoxy-1-xylose could be isolated. No further attempts were made to isolate any 2-deoxy-pentose present, since it was evident that even if they were successful the method would hardly be of preparative value.

In the preparation of β -methyl-1-arabopyranoside a considerable amount of a syrupy mixture of the α - and the β -isomer was left after removal of the crystalline β -compound. This syrup was condensed with acetone and the product tosylated. After separation of a quantity of the crystalline 2-*p*-tosyl 3:4-isopropylidene β -methyl-1-arabopyranoside the residual syrup was subjected to mild hydrolysis; from the resulting syrup 2-*p*-tosyl α -methyl-1-arabopyranoside was isolated. By methods exactly analogous to those used above in the β -series this compound

was converted into 2:3-anhydro- α -methyl-1-ribose, the latter reacted with sodium thiomethoxide, and the product treated with Raney nickel. The resulting syrup gave analytical values corresponding to a deoxy-methylpentoside, and from the fact that it consumed ca. 0.3 mol./mol. of periodate on titration it appeared to be a mixture of (VII) with a smaller amount of a 2-deoxy-compound; on hydrolysis and treatment of the product with *p*-nitrophenylhydrazine only 3-deoxy-1-xylose *p*-nitrophenylosazone was isolated. This was rather surprising in view of the periodate titration value mentioned above, but it is possible that this value may give an exaggerated estimate of the content of 2-deoxy-pentoside in the mixture.

The results obtained indicate that the projected route to 2-deoxyribose from arabinose via the 2:3-anhydroarabinosides is unlikely to be of any practical interest if, indeed, it can be realised. The route, however, does form a fairly convenient method for the preparation of 3-deoxy-1-xylose and its derivatives, since the overall yield from methyl-1-arabopyranoside is very satisfactory. Other possible routes to 2-deoxyribose derivatives are under investigation and will be reported upon in due course.

EXPERIMENTAL.

β -Methyl-1-arabopyranoside.—Following the procedure of Hudson (*J. Amer. Chem. Soc.*, 1925, **47**, 267) we obtained from *l*-arabinose (100 g.) pure β -methyl-1-arabopyranoside (32 g.), together with a syrupy mixture of the α - and the β -isomer (ca. 75 g.).

3:4-isopropylidene β -Methyl-1-arabopyranoside.—To an ice-cold suspension of finely powdered β -methyl-1-arabopyranoside (32 g.) in dry acetone (750 c.c.), phosphoric oxide (26 g.) was gradually added with stirring. The temperature was kept below 5° and stirring continued until the starting material dissolved (ca. 3 hours), then set aside overnight in the refrigerator. The supernatant liquid was decanted from the mixture of phosphoric acid, etc., which had settled to the bottom of the flask, and neutralised by gradually adding concentrated aqueous potassium hydroxide. The mixture was filtered and the filtrate concentrated under reduced pressure (bath temp. 35°). The syrupy product was distilled at 80–90° (bath temp.)/5 \times 10⁻⁴ mm. giving the isopropylidene derivative as a colourless syrup (29 g.; 72.5%). $[\alpha]_D^{20} +175.7^\circ \pm 0.5^\circ$ (c, 5.2 in chloroform) (Found: C, 53.3; H, 7.7. C₁₃H₁₈O₅ requires C, 52.9; H, 7.8%). The same product was obtained although in much lower yield by carrying out the condensation of β -methyl-1-arabopyranoside with acetone in presence of anhydrous copper sulphate and sulphuric acid.

2-p-Tosyl 3:4-isopropylidene β -Methyl-1-arabopyranoside.—*p*-Tosyl chloride (28.5 g.) was added to a solution of 3:4-isopropylidene β -methyl-1-arabopyranoside (27.3 g.) in dry pyridine (136 c.c.) and the mixture warmed at 40° for 24 hrs. A small amount of water (1 c.c.) was added, and the solution set aside at 0° for 30 minutes. More water (ca. 100 c.c.) and chloroform (ca. 250 c.c.) were added and the mixture was shaken. The chloroform layer was separated, and the aqueous layer extracted several times with small quantities of chloroform. The combined chloroform extracts were washed successively with ice-cold dilute sulphuric acid, sodium hydroxide, and water, dried (Na₂SO₄), and evaporated under reduced pressure. The residue recrystallised from alcohol gave colourless rod-shaped prisms (37.5 g.), m. p. 133°, $[\alpha]_D^{20} +187.3^\circ \pm 2^\circ$ (c, 1.55 in chloroform) (Found: C, 53.8; H, 6.1; S, 8.6. C₁₈H₂₂O₅S requires C, 53.6; H, 6.2; S, 8.9%).

2-p-Tosyl β -Methyl-1-arabopyranoside.—A solution of 2-p-tosyl 3:4-isopropylidene β -methyl-1-arabopyranoside (34 g.) in a mixture of methanol (1400 c.c.) and dilute sulphuric acid (280 c.c. of N) was heated at 40° for 4 hours; a further quantity of sulphuric acid (280 c.c. of N) was then added and the solution maintained at 40° for a further 4 hours, then cooled and neutralised by shaking with precipitated barium carbonate. Filtration followed by removal of solvents under reduced pressure (bath temp. 40°) gave a syrup which was taken up in ether; the solution was dried (Na₂SO₄) and evaporated. The residue solidified on removal of the last traces of solvent in a vacuum. The product (30 g.) could be purified by precipitation from ethereal solution with pentane; it then had m. p. ca. 43°, but was very hygroscopic. $[\alpha]_D^{20} +115^\circ \pm 1^\circ$ (c, 3.47 in chloroform) (Found: C, 49.1; H, 5.9. C₁₃H₁₈O₅S requires C, 49.0; H, 5.7%).

2:3-Anhydro- β -methyl-1-ribose.—Ice-cold methanolic sodium methoxide (75 c.c. of a solution prepared by dissolving 6 g. sodium in 100 c.c. methanol) was added to a solution of 2-p-tosyl β -methyl-1-arabopyranoside (28.2 g.) in chloroform (350 c.c.) at 0°, and the mixture set aside in the refrigerator for 3 days with occasional shaking, then left at room temperature for a further 24 hours and neutralised with *N*-sulphuric acid. The chloroform layer was separated and the aqueous layer extracted with chloroform, and the combined chloroform extracts were dried (Na₂SO₄) and evaporated under slightly reduced pressure (bath temp. 40°). The anhydro-glycoside was obtained as a colourless syrup (11.4 g.), which on being kept in a desiccator over phosphoric oxide slowly set to a mass of needles which were so hygroscopic that a satisfactory m. p. determination could not be made. $[\alpha]_D^{20} +35.7^\circ \pm 1^\circ$ (c, 2.7 in chloroform) (Found: C, 49.3; H, 6.9. C₈H₁₀O₄ requires C, 49.3; H, 6.9%).

3-Methylthio β -Methyl-1-xylopyranoside.—2:3-Anhydro- β -methyl-1-ribose (5 g.) was dissolved in methanolic sodium thiomethoxide (37.5 c.c. containing 1.87 g. of sodium and 5 g. of methylthiol) and the solution refluxed for 2 hours, then cooled, exactly neutralised with *N*-sulphuric acid, and evaporated to dryness under reduced pressure (bath temp. 40°). The residue was extracted with chloroform, and the extract dried (Na₂SO₄) and evaporated. The brownish syrup (6.9 g.) could be purified by chromatography on active alumina in benzene solution; a small amount of material passed through the column, and elution of the adsorbed material with methanol gave the product (0.8 g. from 1 g.) as a faintly yellow syrup (Found: C, 43.2; H, 7.2. C₇H₁₄O₄S requires C, 43.3; H, 7.3%).

3-Deoxy- β -methyl-1-xylopyranoside.—(1) From 3-methylthio β -methyl-1-ribosepyranoside. The crude methylthio-compound (6 g.) was dissolved in a mixture of alcohol (300 c.c.) and water (70 c.c.), and

Raney nickel (150 g. prepared according to Mzingo *et al.*, *loc. cit.*) added. The mixture was heated under reflux for 2 hours and filtered, the nickel being thoroughly washed with alcohol, and the combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in water (35 c.c.), the solution thrice extracted with chloroform, and the aqueous phase evaporated under reduced pressure (bath temp. 40°) to a syrup, which was dissolved in acetone (30 c.c.) and filtered from inorganic material, and the acetone again evaporated under reduced pressure. The residue so obtained distilled at 110° (bath temp.)/ 4×10^{-3} mm. as a colourless hygroscopic syrup (3.6 g.). $[\alpha]_D^{25} + 142.2^{\circ} \pm 5^{\circ}$ (c. 2.25 in chloroform) (Found: C, 48.0; H, 8.5. $C_6H_{12}O_4$ requires C, 48.6; H, 8.2%). The product was virtually unaffected by sodium metaperiodate (0.2163 g. consumed 0.02 c.c. of M-periodate in 24 hours; 0.07 c.c. in 48 hours) but it gave a feeble green coloration in the Keller-Kiliani test.

(2) From 2: 3-anhydro- β -methyl-*l*-ribosepyranoside. Raney nickel (4 g.) was added to the anhydro-compound (3.3 g.) dissolved in alcohol (60 c.c.) and the mixture hydrogenated at $110^{\circ}/100$ atm. during 24 hours. Catalyst was removed by filtration and the filtrate evaporated under reduced pressure, yielding a colourless syrup which distilled at $100-105^{\circ}$ (bath temp.)/ 10^{-3} mm. The product (2.2 g.) had $[\alpha]_D^{25} + 143^{\circ} \pm 4^{\circ}$ (c. 2.868 in chloroform) (Found: C, 48.7; H, 8.3; OMe, 19.9. $C_6H_{12}O_4$ requires C, 48.6; H, 8.2; OMe, 20.9). It gave a weak colour in the Keller-Kiliani test, and on titration with periodate it took up 0.17 mol. of reagent in 48 hours, suggesting that it may have been contaminated with some of the corresponding 2-deoxy-riboside.

3-Deoxy-1-xylose.—The syrupy glucoside obtained by method (1) above (0.3868 g.) was heated to 100° with dilute sulphuric acid (25 c.c. of 0.5N) until a constant rotation was attained (75 minutes). Specific rotations: after 60 minutes, $+8.4^{\circ}$, after 75 minutes, $+7.9^{\circ} \pm 1.5^{\circ}$ (constant). The solution was neutralised with freshly precipitated barium carbonate, filtered, and evaporated under reduced pressure. The residual syrup was evaporated once under reduced pressure with methanol and dissolved in absolute alcohol. Inorganic matter was precipitated by addition of ether and the solution evaporated under reduced pressure yielding the sugar as a colourless syrup which immediately reduced Fehling's solution but could not be crystallised (Found: C, 44.4; H, 7.7. $C_6H_{10}O_4$ requires C, 44.8; H, 7.5%). Calculated from the final rotation of the hydrolysis solution the sugar had $[\alpha]_D^{25} + 8.7^{\circ} \pm 1.5^{\circ}$.

A similar product was obtained by hydrolysing a sample of 3-deoxy- β -methyl-*l*-xylopyranoside prepared by method (2) above; the specific rotation became constant after 90 minutes at $+9^{\circ}$.

3-Deoxy-1-xylose *p*-Nitrophenylosazone.—This was prepared by heating 3-deoxy-1-xylose (230 mg. prepared *via* the methylthio-compound) in water (6 c.c.) with *p*-nitrophenylhydrazine (600 mg.) in glacial acetic acid (1 c.c.) for 1 hour on the steam-bath, and recrystallised from alcohol; dark red micro-crystalline powder, m. p. $254-256^{\circ}$ (Found: C, 51.2; H, 4.8; N, 20.9. $C_{11}H_{18}O_8N_2$ requires C, 50.7; H, 4.6; N, 20.9%). Similar treatment of a sample of the sugar prepared by the procedure involving hydrogenolysis of the anhydro-compound gave the same product, no other product could be isolated, although the m. p. of the crude osazone was somewhat lower.

1-erythro-1:3:4-Trihydroxyvaleric Acid Phenylhydrazide.—Bromine (0.25 c.c.) was added to a solution of 3-deoxy-1-xylose (470 mg.) in water (6 c.c.) and the mixture shaken in a closed vessel for 48 hours in the dark. Unchanged bromine was then removed under reduced pressure in a stream of air, the solution neutralised with freshly precipitated silver carbonate, and excess of silver removed with hydrogen sulphide. The solution obtained by filtering through charcoal was evaporated under reduced pressure and the residue evaporated once with methanol. The syrup (370 mg.) so obtained was lactonised by distillation at 120° (bath temp.)/ 3×10^{-4} mm. and the syrupy lactone (114 mg.) heated for 30 minutes at 100° with phenylhydrazine (100 c.mm.). After 3 hours a semi-crystalline mass had separated; ether was added and the colourless crystalline precipitate filtered off. Recrystallised from alcohol the hydrazide formed colourless needles, m. p. 149° , $[\alpha]_D^{25} + 4.5^{\circ} \pm 5^{\circ}$ (c. 0.4 in alcohol) (Found: N, 11.7. Calc. for $C_{11}H_{16}O_4N_2$: N, 11.7%). Nef (*loc. cit.*) records for *d*-erythro-1:3:4-trihydroxyvaleric acid phenylhydrazide, m. p. 150° and $[\alpha]_D^{25} + 9.4^{\circ}$.

2-*p*-Tosyl α -Methyl-*l*-arabopyranoside.—The syrupy residue remaining after removing the crystalline β -methyl-*l*-arabopyranoside from the glycosidisation mixture from 100 g. of *l*-arabinose was condensed with acetone (1700 c.c.) in presence of phosphoric oxide (60 g.) as described above for the pure β -compound. The product (40 g.), a mixture of the α - and the β -isomer of 3:4-isopropylidene methyl-*l*-arabopyranoside, distilled at $100-110^{\circ}$ (bath temp.)/ 10^{-3} mm. (Found: C, 52.8; H, 8.0. Calc. for $C_9H_{16}O_6$: C, 52.9; H, 7.8%).

The above α - β -mixture (40 g.) was dissolved in pyridine (200 c.c.) and tosylated as described under the β -compound. The product, a colourless syrup, was dissolved in a minimum amount of alcohol and set aside overnight in the refrigerator. Pure 2-*p*-tosyl 3:4-isopropylidene β -methyl-*l*-arabopyranoside (17.5 g.) separated, m. p. and mixed m. p. 135° . The alcoholic mother liquor gave on evaporation a syrup (42 g.) which was hydrolysed for 8 hours with methanol (1600 c.c.) and dilute sulphuric acid (650 c.c. of N). The hydrolysis solution was neutralised with precipitated barium carbonate, filtered, and evaporated under reduced pressure giving a syrup containing some crystalline material. This product was dissolved in ether, dried (Na_2SO_4), concentrated to ca. 250 c.c., and set aside overnight in the refrigerator. 2-*p*-Tosyl α -methyl-*l*-arabopyranoside separated as colourless needles (5.3 g.), m. p. $129-130^{\circ}$, $[\alpha]_D^{25} - 15.4^{\circ} \pm 0.4^{\circ}$ (c. 4.88 in chloroform) (Found: C, 48.8; H, 5.7; S, 10.2. $C_{12}H_{18}O_6S$ requires C, 49.0; H, 5.7; S, 10.1%). On titration with sodium metaperiodate 1.1 mols. of oxidant were taken up.

2:3-Anhydro- α -methyl-*l*-ribosepyranoside.—Prepared from 2-*p*-tosyl α -methyl-*l*-arabinoside (3.8 g.) in a manner similar to that described above for the β -isomer, the anhydro-compound (1.7 g.) was obtained as a syrup which crystallised on being kept for a few days in a desiccator and then had m. p. ca. 73° (sealed tube); $[\alpha]_D^{25} - 145.1^{\circ} \pm 3^{\circ}$ (c. 1.9 in chloroform) (Found: C, 49.2; H, 6.9. $C_6H_{10}O_4$ requires C, 49.3; H, 6.9%).

When the anhydro-compound (1.7 g.) was treated with methanolic sodium thiomethoxide and the product refluxed in alcohol with Raney nickel as described for the β -isomer, a hygroscopic syrup (1 g.) was obtained which distilled at $100-105^{\circ}$ (bath temp.)/ 10^{-3} mm. and had $[\alpha]_D^{25} - 141.8^{\circ} \pm 1^{\circ}$ (c. 2.48 in chloroform) (Found: C, 48.0; H, 8.0. Calc. for $C_6H_{12}O_4$: C, 48.6; H, 8.2%). It gave a weak green

Keller-Kiliani reaction and on titration with periodate took up ca. 0.3 mol./mol. That it contained 3-deoxy- α -methyl-*l*-xylopyranoside as its major constituent was proved by hydrolysis with 0.5*N*-sulphuric acid (specific rotations: after 20 minutes in the cold, -116° ; after 30 minutes' heating, -3.4° ; after 45 minutes' heating, $+4.5^\circ$ constant) when a syrupy sugar was obtained (Found: C, 44.4; H, 7.7. Calc. for $C_8H_{10}O_4$: C, 44.8; H, 7.5%). Warmed with *p*-nitrophenylhydrazine the sugar yielded 3-deoxy-*l*-xylose *p*-nitrophenylosazone, m. p. 254° undepressed in admixture with an authentic specimen (m. p. $254-256^\circ$) prepared above from the β -methylglycoside; no other crystalline material was isolated.

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[Received, October 18th, 1946.]

184. *An Experimental Study of the Alkylation of Aromatic Amines using (1) Aluminium Alkoxides and (2) Alumina with Alcohols.*

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The alkylation of aniline salts and complexes by means of aluminium alkoxides has been explored, and the influence of various anions and cations present on the rate of alkylation roughly examined. The vapour-phase methylation of methylaniline with methanol in the presence of alumina has also been studied in some detail, together with the effect on the rate of *N*-alkylation and on the tendency towards nuclear alkylation of the addition to the catalyst of various metallic salts.

THE demand for *N*-alkylated amines for war purposes led the authors to a review of alternative methods of alkylation which might be preferable in some respects to those at present used industrially. Some of the experimental results obtained with two such methods are described here. Not enough evidence is available to indicate whether the two processes under consideration differ fundamentally from one another or whether either or both of them involve the same reacting entities as the other known alkylation processes. It would therefore be premature to introduce a theoretical discussion at this stage. The catalytic action of alumina presents many points of interest which have often been discussed in the literature. Further information will no doubt be gained from a strictly quantitative study of the vapour-phase alkylation process. Requirements of such a study include rigid temperature control and a constant rate of passage of the reaction mixture over the catalyst. The considerable mechanical difficulties involved in meeting these requirements are gradually being overcome and it is hoped that the experimental results eventually obtained will be precise enough to justify theoretical treatment. Meanwhile, many of the facts brought to light during our preliminary studies seem to be of sufficient interest to describe here.

(1) *Alkylation of Aniline Salts and Complexes with Aluminium Alkoxides.*—Lazier and Adkins (*J. Amer. Chem. Soc.*, 1924, 46, 741) described the successful alkylation of aniline by heating it with the requisite aluminium alkoxide in a sealed tube at $250-350^\circ$. It is possible, however, to alkylate salts of aniline or aniline-metallic salt complexes under atmospheric pressure with aluminium alkoxides at considerably lower temperatures than those needed for aniline itself. The following table summarises a series of experiments in which various aniline salts were mixed with four times the amount of aluminium ethoxide required for complete diethylation and heated under a reflux condenser for several hours. The ease of alkylation of the iodide is

Salt.	Temp.	Time, hours.	Primary base in product, %.
Ph·NH ₂ Cl	184°	5	91.8
Ph·NH ₂ Br	184	5	46.7
Ph·NH ₂ I	184	5	2.4 *
Ph·NH ₂ Br	198	5½	6.3
(Ph·NH ₂) ₃ PO ₄	198	5½	91.3
(Ph·NH ₂) ₂ SO ₄	240	5	30.0

* Tertiary base 18.6%.

remarkable but is in agreement with a recorded observation that the direct action between alcohols and aniline is catalysed by iodides (Brit. Pat. 145,743).

Complexes of aniline with metallic salts can also be ethylated by a similar procedure, but the reaction does not take place as readily as with the anilinium salts:

Complex.	Temp.	Time, hours.	Primary base in product, %.
CdSO ₄ ·2Ph·NH ₂	240°	5	69.8
ZnSO ₄ ·2Ph·NH ₂	240	5	80.3
ZnCl ₂ ·2Ph·NH ₂	240	5	56.2
ZnBr ₂ ·2Ph·NH ₂	240	5	41.8
NiCl ₂ ·2Ph·NH ₂	240	5	90.3

It is evident that both cations and anions have an influence on the rate of alkylation.

The addition of sodium halides to reaction mixtures containing anilinium halides generally increased the rate of alkylation:

Anilinium salt.	Added salt.	Temp.	Time, hours.	Primary base in product, %.
Ph·NH ₃ Cl	NaCl (1 mol.)	184°	5	44·1
Ph·NH ₃ Cl	NaCl (2 mols.)	184	5	27·4
Ph·NH ₃ Br	NaBr (1 mol.)	183	5	43·6
Ph·NH ₃ Br	NaBr (1·5 mols.)	184	5	34·3

Some experiments on the *n*-butylation of aniline hydrochloride were made in which the different sodium halides were used as catalysts:

Na halide per mol. of Ph·NH ₃ Cl.	Temp.	Time, hours.	Composition of basic product:		
			Primary, %.	Secondary, %.	Tertiary, %.
NaCl (1 mol.)	198°	16	65·1	34·9	—
NaBr (1 mol.)	198	10	43·3	48·7	8·0
NaI (1 mol.)	198	10	3·3	64·0	32·7

The following routine was adopted for isolating and examining the products from all experiments. The reaction mixture was mixed with a concentrated solution of sodium hydroxide and steam-distilled until no further oil came over. The distillate was extracted thoroughly with ether, and the ethereal solution dried with sodium sulphate. After removal of the ether the bases were distilled. If the distillation temperature indicated that no high-boiling fraction was present, the absence of important amounts of tertiary amine was assumed and no attempt was made to estimate it. Aniline in the product was determined by taking advantage of the fact that it forms a stable complex CdCl₂·Ph·NH₃, precipitated when it is shaken with a saturated aqueous solution of cadmium chloride. The secondary and tertiary bases do not form water-stable complexes with cadmium chloride. For the actual estimation about 1 g. of the mixed bases was weighed in a 25-ml. graduated flask and 20 ml. of light petroleum (b. p. 40—60°) added with just sufficient 1:4-dioxan to form a homogeneous solution. The volume was then made up to 25 ml. with more light petroleum. Then 2 ml. of this solution, or more if the aniline content was low, were run into a small separating funnel and shaken with 3 ml. of saturated cadmium chloride solution. The white complex salt was immediately precipitated together with some cadmium chloride. Generally, most of the precipitate adhered to the wall of the funnel. The liquid was run off through a fritted-glass filter, and the precipitate remaining, partly in the funnel and partly on the filter, was washed with a little light petroleum. The precipitate was then dissolved in 10% hydrochloric acid and titrated with standard bromide-bromate solution and thiosulphate, and the result calculated as aniline. When the preliminary distillation showed the presence of much tertiary amine the above procedure was supplemented by an acetylation of the total bases with a known weight of acetic anhydride and determination of the amount unused after half an hour by decomposition with water and titration with alkali.

(2) *The Vapour-phase Methylation of N-Methylaniline by Methanol in the Presence of an Alumina Catalyst.*—Mailhe and de Godon (*Compt. rend.*, 1918, 166, 467, 564; 1920, 171, 1154; 1921, 172, 1417) successfully alkylated aromatic amines by passing the mixed vapour of the amine and the requisite alcohol over a heated alumina catalyst. The reaction was further studied by Schujkin, Balandin, and others (*J. Gen. Chem. Russ.*, 1934, 4, 1444; *J. Physical Chem.*, 1935, 39, 1192), especially in respect of the effect of other oxides in admixture with the catalyst. In general, the other oxides diminished the activity of the catalyst, but were sometimes beneficial in inhibiting side reactions.

The large-scale manufacture of alkylated anilines by vapour-phase catalytic methods was successfully practised during the war. With suitably chosen catalysts, much lower temperatures than those specified by the above-mentioned workers (350—400°) were effective in bringing about a high degree of alkylation. It was, therefore, of interest to study the reaction more closely and especially to search for promoters which would increase the activity of the catalyst. To enable large numbers of experiments to be performed in reasonable time, their scale was kept as small as possible. The methods used for the analysis of the products were chosen for their rapidity and reproducibility rather than for their absolute accuracy. The experiments here described were exploratory and only roughly quantitative and were intended to give the preliminary information needed for planning more strictly quantitative work on the reaction. However, they themselves led to definite and interesting conclusions, which justify their description at this stage.

The apparatus used was simple. The liquid mixture of alcohol and amine (with any miscible promoting agent, if used) was placed in a feed chamber terminating in a capillary which projected well into the catalyst tube. A finely adjustable pressure of nitrogen was maintained above the reaction mixture to regulate its speed of introduction, and a by-pass also admitted a regulated stream of nitrogen into the catalyst tube. The tube itself was 35 cm. long and 13 mm. in diameter and terminated in a beak to facilitate the collection of the products in a small flask. The temperature of the catalyst mass was observed by means of a thermometer immersed in it. The tube was heated in an electric furnace.

To avoid unnecessary complications in the analysis of the products, attention was concentrated on the second stage of the methylation of aniline, namely, the conversion of *N*-methyl- into *NN*-dimethylaniline. Accompanying this reaction there is also some nuclear alkylation, the amount of which varies considerably according to the catalyst and experimental conditions used. The principal nuclear alkylation product to be expected is *N*-methyl-*p*-toluidine because it is known that in the large-scale methylation and ethylation of aniline the nuclear by-products consist mainly of *N*-methyl-*p*-toluidine and *N*:*p*-diethylaniline respectively [private communication from F. Kaufer and (Miss) J. Fildes]. A rapid, approximate method of determining the amounts of *N*-methylaniline, *N*-methyl-*p*-toluidine, and *NN*-dimethylaniline in the presence of one another depends on a combination of acetylation and refractive-index measurement. The secondary bases can be determined by quantitative acetylation, and the sum of *N*-methyl-*p*-toluidine and *NN*-dimethylaniline by measurement of the refractivity of the mixed bases. The refractive indices (n_D^{20}) of the three bases are: *N*-methylaniline, 1.5714; *NN*-dimethylaniline, 1.5587; *N*-methyl-*p*-toluidine, 1.5582.

The catalytic activity of alumina, it is well known, varies greatly with the method of preparation. For these experiments, with a few exceptions specifically mentioned, the catalyst was made by decomposing aluminium *n*-butoxide with water, and drying and heating the product at 400° for 2 hours. It was then broken up and sifted, the fraction passing a 10-mesh and retained by a 20-mesh sieve being used. The weight of catalyst used for each experiment was 3 g., occupying approximately 10 c.c.

When the effect of a promoter in the catalyst itself was being examined, a quantity equivalent to 0.5 g. of sodium iodide was dissolved in methanol or aqueous methanol and mixed with 3 g. of the alumina, the solvent being then removed by heating on a water-bath.

For each of the experiments tabulated below, a reaction mixture containing 2 g. of *N*-methylaniline and 0.6 g. of methanol was introduced during 3½ hours into the catalyst tube, heated at 250° unless otherwise specifically mentioned.

In view of the accelerating effect of iodides in the alkylation of aniline salts by aluminium alkoxides mentioned above, a series of experiments were made using iodine or iodides in the reaction mixture. The percentage of acetyltable bases in the product was determined and calculated as monomethylaniline. The same charge of catalyst was used for the whole series of 11 experiments.

Amt. of iodine or iodide added.	Acetyltable bases expressed as NHPhMe, %.	Amt. of iodine or iodide added.	Acetyltable bases expressed as NHPhMe, %.
(None)	73.0	None	59.0
0.5% CH ₃ I	67.5	None	64.0
0.9% CH ₃ I	57.2	None	70.0
1.0% NH ₂ PhMeI	46.5	1% I	56.5
1.5% NH ₂ PhMeI	46.5	1% I	49.3
None	52.0		

These results show that iodine and iodides have a strongly accelerating effect on the reaction and that the effect is retained by the catalyst for some time.

When *N*-methylanilinium chloride is added to the reaction mixture there is not a marked increase in *N*-alkylation but a certain amount of nuclear alkylation takes place. The catalyst in this group of experiments was that used on the manufacturing scale for the methylation of aniline.

NH ₂ PhMeCl added, %.	NHPhMe in product, %, from refractivity.	Acetyltable bases, %, calc. as NHPhMe.	Diff. due to nuclear alkylation.
None	43	42	- 1
None	42	43	1
None	45	49	4
5%	38	43	5
None	25	40	15
None	31	43	12
None	38	44	6
None	38	45	7
2½%	38	44	6
2½%	39	41	2
2½%	38	53	15
None	38	47	9
None	37	43	6
None	43	42	- 1

It is clear from the above two series of experiments that a lag must be expected when a promoter is introduced with the reaction mixture, the promoted catalyst not showing its full activity for some time. The second series also shows what degree of accuracy is to be expected from the method described for estimation of nuclear alkylation.

A third series of experiments shows the effect of adding to the catalyst itself various salts which might be expected to have some effect in increasing the activity of the catalyst or in promoting nuclear alkylation. Each group of four experiments, three at 250° and one at 290°, was done with one charge of catalyst, a fresh charge being then introduced for the next group.

Temp.	Salt added.	NHPhMe, % from refrac-tivity.	Acetyl-atable bases, % as NHPhMe.	Diff. (nuclear alkyl-ation).	Temp.	Salt added.	NHPhMe, from refrac-tivity.	Acetyl-atable bases, % as NHPhMe.	Diff. (nuclear alkyl-ation).
250°	None	34.2	38.0	3.8	250°	CoCl ₂	10.3	13.1	2.8
250	None	38.9	45.3	6.4	250	CoCl ₂	9.9	19.0	9.1
250	None	41.2	41.9	0.7	250	CoCl ₂	7.5	23.6	16.1
290	None	16.4	19.4	3.0	290	CoCl ₂	17.9	70.9	53.0
250	NaCl	32.7	27.6	— 5.1	250	MnCl ₂	10.4	11.1	0.7
250	NaCl	32.7	31.8	— 0.9	250	MnCl ₂	6.8	20.4	13.6
250	NaCl	33.5	35.1	1.6	250	MnCl ₂	9.0	25.2	16.2
290	NaCl	15.0	30.0	15.0	290	MnCl ₂	0.0	60.6	60.6
250	NaBr	10.4	10.2	— 0.2	250	ZnCl ₂	19.5	21.9	2.4
250	NaBr	11.8	21.2	9.4	250	ZnCl ₂	18.0	—	—
250	NaBr	10.3	21.4	11.1	250	ZnCl ₂	10.4	35.5	25.1
290	NaBr	0.6	58.4	57.8	290	ZnCl ₂	6.8	71.1	64.3
250	NaI	17.7	15.6	— 2.1	250	CdCl ₂	9.8	13.0	3.2
250	NaI	17.7	17.9	0.2	250	CdCl ₂	3.5	23.8	20.3
250	NaI	13.3	11.7	— 1.6	250	CdCl ₂	0.5	41.3	40.8
290	NaI	4.5	65.1	60.6	290	CdCl ₂	42.0	71.4	29.4
250	NiCl ₂	13.4	16.7	3.3	250	FeCl ₃	4.5	25.0	20.5
250	NiCl ₂	15.6	22.2	6.6	250	FeCl ₃	15.0	43.7	28.7
250	NiCl ₂	22.5	26.3	3.8	250	FeCl ₃	16.4	40.5	24.1
290	NiCl ₂	14.0	56.0	42.0	290	FeCl ₃	15.6	58.2	42.6
250	CuCl ₂	11.2	43.3	32.1	250	SnCl ₂	9.0	21.8	22.8

Although the figures in the above table show certain obvious irregularities, and minor variations in the values in cols. 3 and 5 cannot be regarded as having any real significance, yet there are major trends which lead to useful conclusions. All the salts used, except sodium chloride, increased the activity of the catalyst at 250°. Raising the temperature from 250° to 290° increased the rate of alkylation with pure alumina and when sodium halides, manganese chloride, or zinc chloride was present; but cobalt and cadmium chlorides definitely depressed the rate of alkylation at the higher temperature. Whilst with pure alumina there is no significant amount of nuclear alkylation even at 290°, yet most of the added salts promoted nuclear alkylation at that temperature and sometimes at 250° also.

The practical experience gained with the simple apparatus showed clearly that for a quantitative study of the kinetics of the alkylation reaction it would require much modification. This work has been undertaken and will be described in a later paper.

The authors' thanks are due for the award of a Commonwealth Government Scholarship to one of them (N. G. H.).

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[Received, October 17th, 1946.]

185. Reactions of Alkylisoformanilides. Part III. With Phenols.

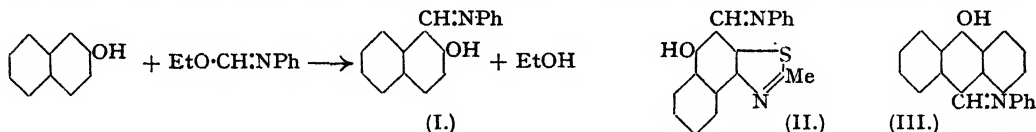
By EDWARD B. KNOTT.

Ethylisoformanilide will react with polycyclic phenols containing a free, active *o*- or *p*-position to form hydroxyanils. Phenol does not react, but various substituted monocyclic phenols showed slight activity. The reagent may be formed *in situ* by using mixtures of ethyl orthoformate and aniline or diphenylformamidine. Replacement of the aniline by other aromatic amines leads to analogues. The reaction may be used as a qualitative test for reactive phenols since all the anils are highly coloured.

In Parts I and II (*J.*, 1945, 686; *J.*, 1946, 120) of this series the activity of alkylisoformanilides towards substances containing reactive or ionisable hydrogen has been described. It was of interest to determine the reactivity of these reagents towards polycyclic phenols, since the latter contain both ionisable and reactive hydrogen atoms.

Although phenol did not react with ethylisoformanilide at temperatures up to 220°, the naphthols showed considerable reactivity even in boiling ethanol, and particularly at temperatures above 100°. The product from β -naphthol, an intensely yellow compound, was homogeneous, and was 2-hydroxy-1-naphthaldehyde anil (I). The orange solid from α -naphthol appeared to be a mixture of anils. The naphthols function therefore like substances containing a reactive methyl or methylene group, and the reaction is not dissimilar to the coupling with

diazonium salts. A variety of phenols were then heated with the reagent, the formation of colour being taken as an indication of reaction. Amongst the monocyclic phenols, the cresols and polyhydroxybenzenes all gave yellow colours but no products were isolated. Polycyclic phenols with active *o*- or *p*-positions gave colours varying from yellow to red. Substances of this type not containing an active hydrogen in the *o*- or *p*-position, such as 1-bromo-2-naphthol,



8-hydroxyquinoline, 4'-hydroxy-2:3'-dimethylnaphtha-1':2':4:5-thiazole, or 2-acetyl-1-naphthol, did not give any colour. Two other anils were isolated, *viz.*, 4'-hydroxy-2-methyl-naphtha-1':2':4:5-thiazole-3'-aldehyde anil (II) and 9-hydroxy-10-anthraldehyde anil (III). The latter gave an intense red solution in aqueous sodium hydroxide. Its solution in acetic acid developed a similar intense red colour on the addition of concentrated hydrochloric acid, the colour fading rapidly as hydrolysis to the aldehyde occurred. The aldehyde differed in m. p. from that given in F.P. 648,069 for the product obtained from 9-hydroxyanthracene formomethylanilide and phosphorus oxychloride; but since in no case was reaction observed where both *o*- and *p*-positions were blocked, it is most likely that the aldehyde group in the present substance was introduced into the 10-position. Somewhat lower yields of anil may be obtained by the formation of the reagent *in situ*. This can be achieved (*cf.* Claisen, *Annalen*, 1895, 287, 365) by fusing the phenol with mixtures of aniline or diphenylformamidine and ethyl orthoformate. Other aromatic amines may replace the aniline to give analogues.

Substance.	Colour.
Phenol	None
<i>m</i> -Cresol	Yellow
<i>o</i> - and <i>p</i> -Cresol	Faint yellow
Resorcinol	Yellow
Adrenalin.....	Red
<i>o</i> -Hydroxybenzylideneacetone	Yellow
2:5-Dihydroxydiphenyl	Orange-yellow
β -Naphthol	Yellow
α -Naphthol	Orange
1:5-Dihydroxynaphthalene	"
1-Bromo-2-hydroxy-naphthalene.....	None
1-Hydroxy-2-acetylnaphthalene	"
1-Hydroxy-4-phenylnaphthalene	Yellow
1-Hydroxy-4-furylnaphthalene-3-carboxylic acid	"
9-Hydroxyanthracene	Orange-red
4-Hydroxy-7-phenylcoumarone-6-carboxylic acid	Yellow
8-Hydroxyquinoline	None
2-Amino-6-hydroxypyridine sulphate	Orange
Aesculin	"
2-Hydroxy-3:4-benzfluorene	Red
4'-Hydroxy-2-methylnaphtha-1':2':4:5-thiazole	Orange-red
2-Acetamido-4'-hydroxynaphtha-1':2':4:5-selenazole	Red
4'-Hydroxy-2:3'-dimethylnaphtha-1':2':4:5-thiazole	None
4'-Hydroxy-2-methylphenanthra-1':2':4:5-thiazole	Red
1'-Hydroxy-2-methylphenanthra-4':3':4:5-thiazole	"
4'-Hydroxy-2-methylthionaphtheno-7':6':4:5-thiazole	Orange

The reaction may be used as a sensitive test for many phenols since the reaction products are highly coloured. The table indicates the colours obtained on boiling a small quantity of the phenol with an excess of reagent in a test-tube over a free flame.

EXPERIMENTAL.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.'s uncorrected.)

2-Hydroxy-1-naphthaldehyde Anil (I).—(a) β -Naphthol (14.4 g.; 0.1 mol.) and ethylisoformanilide (14.9 g.; 0.1 mol.) were fused at 160° for 30 minutes, by which time the evolution of ethyl alcohol had ceased. Methyl alcohol (5 c.c.) was added to the melt. The yellow solid (17.0 g., 81%) crystallised as glossy needles, m. p. 92°, with an intense green fluorescence to ultra-violet light, when the methyl alcoholic solution was chilled, or shiny plates, m. p. 92°, with no fluorescence in ultra-violet light, if the same solution were allowed to cool (Found: C, 82.3; H, 5.4; N, 5.75. Calc. for C₁₇H₁₃ON: C, 82.55; H, 5.3; N, 5.65%).

(b) β -Naphthol (2.88 g.; 0.02 mol.), diphenylformamidine (2.92 g.; 0.02 mol.), and ethyl orthoformate (2.96 g.; 0.02 mol.) were fused at 150° for 60 minutes. After cooling, light petroleum was added and the whole shaken until the melt had solidified. From methyl alcohol (10 c.c.), 2.25 g. (46%) of the anil were obtained. If the ethyl orthoformate is omitted a yellow colour develops but the yield of anil is very low.

2-Hydroxy-1-naphthaldehyde p-Methoxyanil.— β -Naphthol (5.96 g.; 0.04 mol.), ethyl orthoformate (5.92 g.; 0.04 mol.), and *p*-anisidine (4.92 g.; 0.04 mol.) were fused at 145° for 60 minutes. The melt gave a crystalline solid on addition of methyl alcohol. From the same solvent it formed bright yellow needles, m. p. 111°, in 65% yield (Found: N, 5.1. $C_{18}H_{15}O_2N$ requires N, 5.05%).

9-Hydroxy-10-anthraldehyde Anil (III).—9-Hydroxyanthracene (3.84 g.; 0.02 mol.) and ethylisoformanilide (3 g.; 0.02 mol.) were fused at 180° for 60 minutes. Ethyl alcohol (10 c.c.) was added to the red melt, and the orange-red crystalline solid (4.9 g., 82.5%) was collected and washed with alcohol. It formed garnet red crystals, m. p. 204°, from acetic acid (Found: N, 4.95. $C_{21}H_{18}ON$ requires N, 4.7%).

9-Hydroxyanthracene-10-aldehyde. The anil (2 g.) was dissolved in boiling acetic acid (20 c.c.), and concentrated hydrochloric acid (4 c.c.) added. The intense red colour so formed slowly faded as the aldehyde crystallised. It formed flat, creamy needles, m. p. 230° onwards, from benzene (Found: C, 81.3; H, 4.4. $C_{18}H_{10}O_2$ requires C, 81.05; H, 4.55%).

4'-Hydroxy-2-methylnaphtha-1':2':4:5-thiazole-3'-aldehyde Anil (II).—4'-Hydroxy-2-methylnaphtha-1':2':4:5-thiazole (10.75 g.; 0.05 mol.) and ethylisoformanilide (14.9 g.; 0.1 mol.) were fused at 170° for 60 minutes. On cooling, the orange melt solidified. It was ground with alcohol and well washed with the same solvent. It formed orange needles (13.2 g. = 86% yield), m. p. 228°, from benzene (Found: N, 8.5; S, 9.8. $C_{18}H_{14}ON_2S$ requires N, 8.8; S, 9.75%). The aldehyde was obtained by dissolving the anil (2 g.) in dioxan (30 c.c.), adding concentrated hydrochloric acid (10 c.c.) and water (10 c.c.), and heating for 30 minutes on the steam-bath. The solid was dissolved in an excess of 2*N*-sodium carbonate, filtered from a little unhydrolysed anil, and the yellow solution acidified. From ethyl alcohol it formed yellow-green needles, m. p. 160° (Found: S, 13.1. $C_{13}H_6O_2NS$ requires S, 13.2%).

KODAK LIMITED, WEALDSTONE, MIDDLESEX.

[Received, September 26th, 1946.]

NOTE.

Infra-red Spectrum and Structural Diagnosis: Substituted Carbazoles. By R. E. RICHARDS.

THIS note describes an example, not only of the value to the organic chemist of infra-red measurements in structural diagnosis, but also of an experimental method developed in this laboratory for measuring the spectra of very small amounts of material. A sample was received for examination which had been formed by degradation of a substance of which the structure was not completely known. The specimen was a crystalline solid, only 1.5 mg. being available, and was suspected to be a mixture of carbazole and one or more of its methyl derivatives. It was required to determine which methyl derivatives were present and approximately in what proportions.

The experimental method had been mentioned by early workers (see also Thompson, *J.*, 1944, 191), but had not been widely used until it was developed in this laboratory in connection with recent studies on penicillin.

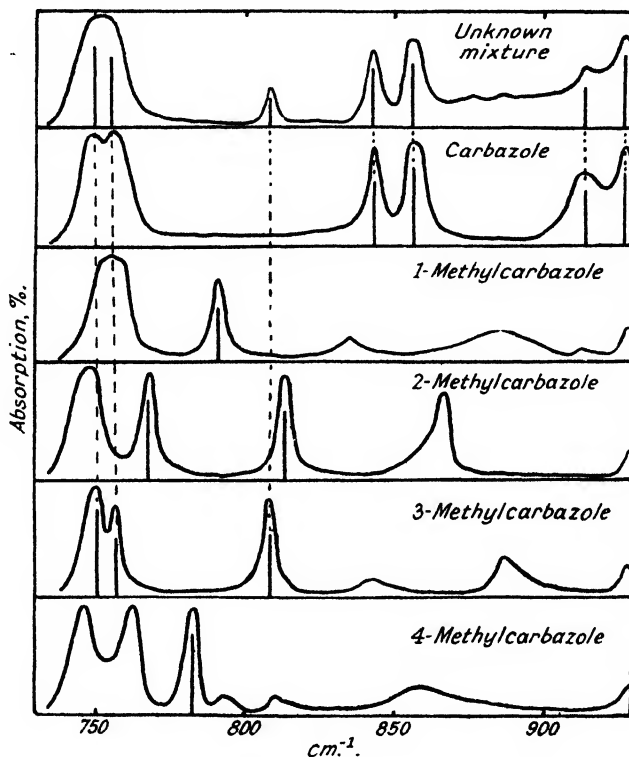
The specimen is ground to a very fine powder in a small glass or agate mortar. A suitable glass mortar can easily be made by rounding off a short piece of narrow glass tubing, and a piece of well-fitting glass rod with rounded end is used as the pestle; a small quantity of dry medicinal paraffin is then added to the powder, and the whole is ground to a smooth paste. This is transferred to a rock-salt plate, about 1.5 × 0.5 cm. in area, and another similar plate is placed on top. With the aid of a small spatula it is possible to prepare the specimen as a long narrow film between the plates, and almost any desired thickness can be obtained by appropriate manipulation, although it is obviously impossible to obtain an exact measure of the thickness of the absorbing layer. No clamping device or spacing washer is necessary, since the surface tension of the oil is sufficient to hold the plates together. The plates are placed on a flat platform so that the film lies exactly at a sharply focused image of the source of radiation, which is usually a Nernst filament. The sample, when thus prepared, causes very little scattering of the infra-red radiation, and a good spectrum can be obtained. The paraffin has strong absorption bands at about 720, 1375, 1460, 2850, 2925 cm^{-1} , but in all other regions of the spectrum it shows no appreciable absorption except in very thick layers. When the spectrum has been measured, a large proportion of the sample can be recovered by extraction with a suitable solvent or by washing away the paraffin with a solvent which does not dissolve the specimen.

This method is often preferable to the alternative procedure of measuring the spectrum in solution; it is very simple, quick, and requires little of the sample. If it is desired to study such a small quantity of a specimen in solution, arrangements must be made to recover it from the solution in the absorption cell, and this requires a rather elaborate technique. This may, however, be essential, since more than one solvent must be used in order to cover the whole range of the infra-red spectrum, no single solvent being available which is completely transparent over the whole spectral range 1–14 μ . Such difficulties imply that in many cases the measurements in solution are impossible. In some circumstances it is useful to study the whole range of the spectrum of the solid as above, then to recover the sample, and to study some particularly interesting region in a suitable solvent which is transparent in that particular range.

The spectrometer used in this problem was a single-beam recording instrument, using a rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268).

Results.—The figure shows the spectrum, over the range 730–930 cm^{-1} , of the unknown mixture,

together with the spectra of pure samples of carbazole and 1-, 2-, 3-, and 4-methylcarbazoles, obtained by the same method. Key bands are emphasised by the vertical lines. The presence of carbazole in the mixture is confirmed by the complete correspondence between the bands in the pure specimen and similar bands in the mixture. The complete absence of bands at either 790 or 782 cm^{-1} indicates the absence of 1- and 4-methylcarbazoles, whereas the band in the mixture at 808 cm^{-1} exactly corresponds to the strong key band of 3-methylcarbazole at this frequency—its weaker band at 886 cm^{-1} is lost between the strong bands of carbazole itself at 856 and 915 cm^{-1} . The strong key bands of 2-methylcarbazole lie rather close to those of 3-methylcarbazole and make it impossible to establish the complete absence of the former, although if it is present, it can only be in very small amounts, for not a trace of the band at



767 cm^{-1} appears in the mixture, and the band at 808 cm^{-1} is not broadened noticeably towards 813 cm^{-1} . It was therefore concluded that the unknown mixture contained mostly carbazole and 3-methylcarbazole. Comparison of the original spectrum with mixtures made from the pure materials shows that the unknown mixture contained between 5% and 12% of 3-methylcarbazole. A closer estimate of the relative proportions was not justifiable owing to the unknown differences in thickness and homogeneity of the different solid samples studied, but if larger amounts of material were available, solutions could be made up and compared with solutions of either the pure components or known match mixtures, so as to obtain a far more exact quantitative estimate.

I should like to thank Mr. K. H. Pausacker, who prepared the pure materials used in this investigation, and the Department of Scientific and Industrial Research for a maintenance grant.—THE PHYSICAL CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD. [Received, October 24th, 1946.]

Twelfth Report of the Committee on Atomic Weights of the International Union of Chemistry.

By G. P. BAXTER (Chairman), M. GUICHARD, O. HÖNIGSCHMID, and R. WHYTLAW-GRAY.

OWING to delays in communication it was impossible for the Committee to publish a report in 1942. The following report therefore covers the two-year period from September 30, 1940, to September 30, 1942. No changes have been made in the table, although the new values for samarium and ytterbium appear to be more reliable than those given in the table.

Carbon.—Murphy and Nier (*Physical Rev.*, 1941, 59, 771) have determined with a mass spectrometer the abundance ratio of ^{12}C to ^{13}C in carbon from different sources to fall between 88.8 and 93.1, corresponding to the values 12.0117 and 12.0112 for the atomic weight of carbon. Both values support the existing chemical evidence that the atomic weight of carbon is very close to 12.01.

Oxygen.—Murphy (*ibid.*, p. 320) with a mass spectrometer finds the abundance ratio of ^{16}O to that of ^{18}O to be 500 ± 15 to 1. This confirms the value of Smythe, 503 ± 10 , and the conversion factor 1.000275.

Fluorine.—Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, 63, 1580) have computed the atomic weight of fluorine from density and X-ray data of lithium fluoride and calcite, using the equation

$$\text{LiF} = \left[\frac{\text{CaCO}_3 \times d_{\text{LiF}}}{d_{\text{calcite}} \times \phi_{\text{calcite}}} \times R^3 \right]$$

where ϕ_{calcite} denotes the volume of a calcite cleavage rhombohedron for which the distance between opposite faces is unity and R denotes the ratio between the true grating spaces for lithium fluoride and calcite.

The following data (20°):

d_{LiF}	2.64030 g./c.c.	Ca	40.075
d_{calcite}	2.71030 g./c.c.	Li	6.939
ϕ_{calcite}	1.09594	C	12.010
R	0.663045		

yield 18.994 for fluorine. If the atomic weight of calcium found by Hönigschmid and Kempter, 40.085, is used, fluorine becomes 18.996.

Zinc.—Hönigschmid and v. Mack (*Z. anorg. Chem.*, 1941, 246, 363) have compared zinc chloride with silver. The zinc chloride was prepared by the action of hydrogen chloride on metal which had been purified by distillation in high vacuum and had been found by Gerlach by optical spectroscopy to be free from all metallic impurities. Further purification by two distillations in hydrogen chloride followed. Comparison of weighed quantities of the chloride with equivalent weights of silver was made by the conventional nephelometric method and the resulting silver chloride also was weighed. Weights are corrected to vacuum.

The Atomic Weight of Zinc.

Preliminary Series.

Wt. of ZnCl_2 , g.	Wt. of Ag, g.	$\text{ZnCl}_2 : 2\text{Ag}$.	At. wt. of Zn.	Wt. of AgCl , g.	$\text{ZnCl}_2 : 2\text{AgCl}$.	At. wt. of Zn.
2.26845	3.59116	0.631676	65.377	4.77125	0.475411	65.383
2.62763	4.15980	0.631672	65.376	5.52705	0.475413	65.374
4.62252	7.31790	0.631673	65.376	9.72300	0.475421	65.377
1.94421	3.07788	0.631672	65.376	4.08936	0.475431	65.380
3.81948	6.04655	0.631679	65.377	8.03341	0.475449	65.385
1.78151	2.82023	0.631690	65.379	3.74741	0.475398	65.370
1.94043	3.07193	0.631665	65.374	4.08179	0.475387	65.367
2.31880	3.67098	0.631657	65.372	4.87719	0.475430	65.382
Average		0.631673	65.376	—	0.475422	65.377

Final Series.

Wt. of ZnCl_2 , g.	Wt. of Ag, g.	$\text{ZnCl}_2 : 2\text{Ag}$.	At. wt. of Zn.	Wt. of AgCl , g.	$\text{ZnCl}_2 : 2\text{AgCl}$.	At. wt. of Zn.
2.08378	3.29875	0.631692	65.380	4.38304	0.475419	65.376
2.39497	3.79141	0.631684	65.378	5.03743	0.475435	65.391
3.25457	5.15229	0.631675	65.376	—	—	—
2.33816	3.70151	0.631678	65.377	4.91803	0.475426	65.378
2.23578	3.53951	0.631664	65.374	4.70270	0.475425	65.378
2.54724	4.03245	0.631686	65.379	5.35790	0.475418	65.376
2.32850	3.68614	0.631691	65.380	4.89779	0.475418	65.376
2.03634	3.22369	0.631680	65.377	4.28307	0.475439	65.382
Average		0.631681	65.378	—	0.475426	65.378

The average of all the experiments, 65·377, confirms the present value in the International Table, 65·38, but is 0·05 unit higher than that calculated from mass spectroscopic data, 65·33.

Molybdenum.—In the tenth report of the Committee the mean mass number as computed by Aston, 96·03, was stated to be in error. This statement is incorrect, and was due to an oversight of the fact that the summation of the percentages of the isotopes as given by Aston is 99·9 instead of 100. With the packing fraction — $6\cdot0 \times 10^{-4}$ and the conversion factor 1·000275 the atomic weight of molybdenum obtained from Aston's mean mass number is 95·95. A more recent determination of the abundance ratios by Valley (*Physical Rev.*, 1940, 57, 945) yields 96·00 and 95·92 as the mean mass number and atomic weight respectively, while Hönigschmid and Wittner by analysis of the pentachloride found 95·95.

Samarium.—Hönigschmid and Hirschbold-Wittner (*Z. physikal. Chem.*, 1941, 189, A, 38) have analysed anhydrous samarium trichloride. The samarium material had been purified by Feit and shown by Noddack by X-ray analysis to be of atomic weight purity. Further purification consisted of double precipitation of the oxalate followed by ignition to oxide in each case and crystallisation of the chloride from solution saturated with hydrogen chloride at ice temperature. The chloride was dehydrated by heating in a current of dry hydrogen chloride at gradually increasing temperatures, finally at 450°. Fusion was avoided since it was found experimentally that dissociation occurs at temperatures above the melting point. After being weighed, the chloride was dissolved and compared with a nearly equivalent weight of pure silver by the usual nephelometric method and the silver chloride was collected and weighed. Weights are corrected to vacuum.

The Atomic Weight of Samarium.

SmCl ₃ fused in HCl.						
Wt. of SmCl ₃ , g.	Wt. of Ag, g.	SmCl ₃ : 3Ag.	At. wt. of Sm.	Wt. of AgCl, g.	SmCl ₃ : 3AgCl.	At. wt. of Sm.
3·27893	4·13279	0·79339	150·403	5·49102	0·59715	150·408
SmCl ₃ dried at 450° in HCl.						
3·08886	—	—	—	5·17381	0·59702	150·354
2·96740	3·74054	0·79331	150·375	4·96975	0·59709	150·385
3·87834	4·88888	0·79330	150·372	6·49574	0·59706	150·371
3·37089	4·24914	0·79331	150·376	5·64562	0·59708	150·380
4·40134	5·54798	0·79332	150·380	7·37129	0·59709	150·385
Average		0·79331	150·376	—	0·59708	150·375

The average of all determinations, 150·38, is 0·05 unit lower than the present international value, 150·43, which depends on analyses of *fused* chloride by Stewart and James (*J. Amer. Chem. Soc.*, 1917, 39, 2605) and Owens, Balke and Kremers (*ibid.*, 1920, 42, 515). Although no change in the table is made at the present time, the new higher value seems to be a more reliable one.

Gadolinium.—Wahl (*Soc. Sci. Fennica, Commentationes Phys.-Math.*, 1941, II, 3, 1) finds the isotopic constitution of gadolinium to be as follows :

Mass	152	154	155	156	157	158	160
Per cent.	0·2	2·86	15·61	20·59	16·42	23·45	20·87

These figures lead to the atomic weight 157·18 if the packing fraction — $1\cdot5 \times 10^{-4}$ is employed.

Ytterbium.—Hönigschmid and Hirschbold-Wittner (*Z. anorg. Chem.*, 1941, 248, 72) have compared anhydrous ytterbium trichloride with silver. The starting material had been prepared by v. Bruckl by repeated electrolytic reduction and when subjected to X-ray analysis by Noddack was found to contain no other rare earths except lutecium, and this element only to the extent of 0·04%. The effect of this impurity would be to raise the atomic weight by only 0·001 unit. After repeated precipitation as hydroxide and oxalate, with intermediate ignition to oxide, the chloride was prepared and crystallised from a solution saturated with hydrogen chloride at 0°. Dehydration in preparation for weighing was effected by heating in a current of dry hydrogen chloride at gradually increasing temperatures up to 450°. Fusion was avoided since Hönigschmid had already found dissociation of the salt to occur above the melting point. Comparison with silver was effected in the usual way with the help of a nephelometer and the resulting silver chloride was collected and weighed. Weights are corrected to vacuum.

The Atomic Weight of Ytterbium.

Wt. of YbCl ₃ , g.	Wt. of Ag., g.	YbCl ₃ : 3Ag.	At. wt. of Yb.	Wt. of AgCl, g.	YbCl ₃ : 3AgCl.	At. wt. of Yb.
3.87107	—	—	—	5.94071	0.649934	173.108
3.82762	—	—	—	5.88965	0.649889	173.089
4.12899	4.78127	0.863576	173.117	6.35269	0.649959	173.119
2.58325	2.99157	0.863510	173.095	3.97473	0.649918	173.101
2.66672	3.08799	0.863578	173.117	4.10299	0.649946	173.113
2.58988	2.99916	0.863535	173.104	3.98478	0.649943	173.112
2.06819	2.39519	0.863476	173.085	—	—	—
2.42097	2.80349	0.863556	173.100	3.72495	0.649934	173.108
2.08411	2.41356	0.863500	173.092	3.20680	0.649904	173.095
1.72464	1.99732	0.863477	173.085	2.65378	0.649881	173.085
3.12912	3.62361	0.863537	173.089	4.81490	0.649883	173.086
3.92599	4.54636	0.863546	173.107	6.04062	0.649932	173.107
4.98554	5.77369	0.863493	173.090	7.67151	0.649877	173.083
Average		0.863526	173.098	—	0.649916	173.100

The average, 173.10, is 0.06 unit higher than that found by Hönigschmid and Striebel (*Z. anorg. Chem.*, 1933, 212, 385) with less pure material isolated by Prandtl. The new, higher value is evidently to be preferred although Wahl (*Naturwiss.*, 1941, 29, 536) by determination of isotopic abundances obtains the lower figure.

Mass	168	170	171	172	173	173	174	176
Per cent.	0.06	4.21	14.26	21.49	17.02	17.02	29.58	13.38

*Thirteenth Report of the Committee on Atomic Weights of the International Union of Chemistry.*¹

By G. P. BAXTER (Chairman), M. GUICHARD, and R. WHYTLAW-GRAY.

IN the very regrettable death of Professor Otto Hönigschmid the International Committee on Atomic Weights has suffered a great loss. Professor Hönigschmid not only very actively promoted the work of the Committee but was himself responsible for a large portion of recent experimental work in this field.

Owing largely to difficulties of communication no report of the International Committee on Atomic Weights has been published for some time. The twelfth report was published only in Germany and France but essentially the same material appeared as the Report of the Committee on Atomic Weights of the American Chemical Society² at about the same time as the German Report.³ Since no changes in the Table of Atomic Weights have been made since the Eleventh Report of the International Committee was published in 1941 until this year, this situation can have caused no serious difficulty. In the Table of Atomic Weights at the end of this report changes have been made in the cases of sulphur and copper. Attention is called to the fact that the atomic weight of common lead as determined from isotopic composition varies with the source over a range of 0.03–0.04 unit. At the present time it seems unwise to try to include values for the new elements Nos. 93–96, neptunium, plutonium, curium and americium.

Beryllium.—Johannsen (*Naturwiss.*, 1943, 31, 592) synthesised beryllium chloride from beryllium oxide and carbon in a stream of chlorine and purified the product by sublimation without melting, first in chlorine, then in nitrogen, and finally in vacuum. The product was collected in sealed glass bulbs and was analysed in the usual way both by comparison with silver and by weighing the silver chloride, with the same resulting atomic weight 9.013 for beryllium. This result is somewhat lower than that found earlier by Hönigschmid and Birkenbach by analysis of the chloride, 9.018, and agrees closely with the mass spectroscopic value 9.0126.

Carbon and Nitrogen.—Casado (Thesis, University of Santiago, 1943) has redetermined experimentally the densities of oxygen, nitrous oxide, and methyl oxide at pressures of one atmosphere and below, as well as the deviations from Boyle's law at low pressures. Corrections of weights to the vacuum standard, for the contraction of the globes at pressures below one atmosphere, and for gravity were made. The average values from a large number of determinations are given in the following table.

	Oxygen.	Nitrous oxide.	Methyl oxide.
$1 + \lambda$	1.00089	1.00710	1.02574
d_1	1.428905	1.97747	2.10809
$d_{\frac{1}{2}}$	1.42844	1.97308	2.08987
$d_{\frac{1}{3}}$	—	—	2.08194
$d_{\frac{1}{4}}$	1.42799	1.96848	2.07330

If the densities plotted against the pressures are assumed to follow a straight line calculated by the method of least squares, the limiting densities and molecular weights are found to be as follows:

	Limiting densities.	Mol. wt.
Oxygen	1.42760	32.000
Nitrous oxide	1.96380	44.019
Methyl oxide	2.0561	46.088

From the molecular weights of nitrous oxide and methyl oxide the atomic weights of nitrogen and carbon may be calculated to be 14.009 and 12.020. If the values of $1 + \lambda$ are used together with the densities at one atmosphere the following results are obtained.

	d_1 .	$1 + \lambda$.	d .	M .
Oxygen	1.428905	1.00089	1.42763	32.000
Nitrous oxide	1.97747	1.00710	1.96352	44.012
Methyl oxide	2.10809	1.02574	2.05518	46.066

from which the atomic weights $N = 14.006$ and $C = 12.009$ result.

Fluorine and Calcium.—In a series of papers, following the first by C. A. Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, 63, 1580), the method of calculating the atomic weights of

¹ Authors of papers bearing on the subject are requested to send copies to each of the three members of the Committee at the earliest possible moment: Prof. G. P. Baxter, Coolidge Laboratory, Harvard University, Cambridge, Mass., U.S.A.; Prof. M. Guichard, Faculté des Sciences, Sorbonne, Paris, France; Prof. R. Whytlaw-Gray, University of Leeds, Leeds, England.

² *J. Amer. Chem. Soc.*, 1943, 65, 1443.

³ *Ber.*, 1943, 76, 35; *Bull. Soc. chim.*, 1944, 11, 214.

fluorine and calcium from density and X-ray data has been continued by Johnston and D. A. Hutchison (*Physical Rev.*, 1943, 62, 32), C. A. Hutchison (*J. Chem. Physics*, 1942, 10, 489), D. A. Hutchison (*Physical Rev.*, 1944, 66, 144), and D. A. Hutchison (*J. Chem. Physics*, 1945, 13, 383). The atomic weights and densities used in the calculations of the last paper are as follows :

Atomic weights.		Densities (20°).	
C	12.0104	C	3.51540
Li	6.9390	LiF	2.64030
Na	22.9970	NaCl	2.16360
Cl	35.4570	KCl	1.98826
K	39.0960	CaCO ₃	2.64030

The most reliable results as given in the last of the papers cited are as follows :

Calcium.

Reference substances.	Assumed atomic weights.	Atomic wt. of Ca.
Calcite, NaCl	Na, Cl, C	40.0851
Calcite, KCl	K, Cl, C	40.0851
Calcite, C (diamond)	C	40.0844
Calcite, LiF	K, Cl, Li, C, Na	40.0850
	Average	40.0849

Fluorine.

Reference substances.	Assumed atomic weights.	Atomic wt. of F.
LiF, KCl	K, Cl, Li	18.9967
LiF, NaCl	Na, Cl, Li	18.9967
LiF, C (diamond)	Li, C	18.9967
LiF, CaCO ₃	Na, Cl, C, Li, K	18.9967
	Average	18.9967

The extraordinary concordance of the above results is of course dependent upon the values assumed in the calculation. If, for instance, the atomic weight of sodium is 22.994, the most recent value determined by Johnson, all molecular weights depending on that of sodium chloride will be lowered by 0.005%, and if the atomic weight of potassium is 39.098 instead of the one used, values depending on potassium chloride will be raised by 0.003%. The effect of this upon the atomic weight of calcium in the first two instances in the above table would be - 0.005 and + 0.002 unit. Because of the small molecular weight of lithium fluoride these uncertainties would affect the atomic weight of fluorine by only 0.001 unit. At the present time these results are to be considered as confirmatory rather than definitive.

Potassium, Aluminium, Magnesium and Sodium.—Batuecas, Casado, and Alonso (*Rev. Real Acad. Cienc. Madrid*, 1944, 38, 349), using the method of Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, 63, 1580), have calculated the atomic weights of potassium, magnesium, aluminium, and sodium. Calcium and carbon are assumed to have the atomic weights 40.080 and 12.010. They find

$$\begin{aligned} \text{K} &= 39.091 \\ \text{Al} &= 26.963 \end{aligned}$$

$$\begin{aligned} \text{Mg} &= 24.317 \\ \text{Na} &= \begin{cases} 22.961 \\ 22.989 \end{cases} \end{aligned}$$

Silicon.—Ney and McQueen (*Physical Rev.*, 1946, 69, 41) and Williams and Yuster (*ibid.*, p. 556) have obtained the following results for the isotopic proportions of silicon :

Isotope	28	29	30
Ney and McQueen	92.24	4.69	3.07
Williams and Yuster	92.27	4.68	3.05

If the packing fractions - 4.86×10^{-4} , - 4.54×10^{-4} and - 5.79×10^{-4} are used the calculated atomic weight is 28.087. This value lies midway between that found by Baxter, Weatherill, and Scripture, 28.063, by comparing the halides with silver, and those obtained by Hönigschmid and Steinheil, 28.105, by the same method, and by Weatherill, 28.103, from the ratio of the tetrachloride to the dioxide.

Sulphur.—Hönigschmid (*Ber.*, 1942, 75, 1814) has redetermined the ratio between silver and sulphur from the synthesis of silver sulphide, by essentially the method used by Hönigschmid and Sachtleben (*Z. anorg. Chem.*, 1931, 195, 207), and with essentially the same result. Weighed quantities of fused buttons of pure silver were heated in a current of nitrogen and the vapour of purified sulphur, then in pure nitrogen at 250–300°. Below 300° the variations in the weight of sulphide were slight. Above 300° both the weight and the appearance of the sulphide were attended with variations. Vacuum corrections were applied.

It is unfortunate that owing to decomposition above 300° the silver sulphide could not be fused in order to make certain of complete conversion, but the fact that repeated heating of the silver sulphide in sulphur vapour at the lower temperature failed to effect appreciable alteration tends to favour the view that the above difficulty was not serious.

In the following table the weights of sulphide are the averages of the concordant observations when the sulphide was heated at various temperatures between 250° and 300°.

Wt. of Ag in vacuum, g.	No. of heatings with S.	Av. wt. of Ag ₂ S in vacuum, g.	Ag ₂ S : Ag.	At. wt. of S.
22-63155	2	25-99501	1-148618	32-0658
23-35829	4	26-82982	1-148621	32-0665
22-64273	1	25-89313	1-148621	32-0671
21-83830	2	25-08394	1-148621	32-0665
21-47088	2	24-66194	1-148623	32-0669
20-98104	4	24-09928	1-148622	32-0663
17-35371	6	19-93282	1-148620	32-0663
16-84347	16	19-34675	1-148620	32-0663
		Average	1-148620	32-0665

Richards and Jones (*J. Amer. Chem. Soc.*, 1907, **29**, 826) from the ratio of silver sulphate to silver chloride found 32-069, while Scheuer (*Sitzungsber. Akad. Wiss. Wien*, 1914, **123**, IIa, 1004) from the ratios $2\text{Ag} : \text{SO}_3 : \text{Ag}_2\text{SO}_4 : 2\text{AgCl}$ obtained the value 32-067. On the basis of the above two investigations by Hönigschmid, especially in view of the extraordinary concordance of the one reported here, there seems little doubt that the atomic weight of sulphur is very close to 32-066 if silver is taken as 107-880, and this value has been adopted for the table in place of the less precise one, 32-06.

Potassium.—Paul and Pahl (*Naturwiss.*, 1944, **32**, 226) have determined the relative abundance of ³⁹K and ⁴¹K in common potassium to be 13.96 ± 0.1 . With the packing fraction -6.1×10^{-4} and the conversion factor 1-000275 the atomic weight of potassium is found to be 39-099. This agrees closely with the average of the most recent determinations of this constant, 39-097.* In the same way a sample of potassium partially separated by ideal distillation by Hevesy and Lögstrup was found to have the atomic weight 39-011. Hönigschmid and Goubeau, and Baxter and Alter both obtained the same value for this sample.

Copper.—Hönigschmid and Johannsen (*Z. anorg. Chem.*, 1944, **252**, 364; *Naturwiss.*, 1942, **31**, 548) have analysed cuprous chloride. Cupric sulphate was crystallised three times in the case of one sample, five times in the case of another. After electrodeposition on a platinum dish at 2 volts, the metal was dissolved in nitric acid and the nitrate crystallised and centrifugally drained. Decomposition to oxide in platinum followed. Spectroscopic examination by Dr. Schöntag revealed no impurities.

Conversion of the cupric oxide into cuprous chloride was carried out in the following operations: drying of the oxide in nitrogen at 200°, reduction in electrolytic hydrogen at 800°, conversion of the metal into cuprous chloride in nitrogen and chlorine mixtures, and resublimation of the cuprous chloride in nitrogen into a weighing tube, all in a quartz bottling apparatus. In the last two steps it was important to avoid a temperature above 600°.

Analysis followed, by solution in ammonia, oxidation to the cupric state with oxygen, acidification with nitric acid and comparison with silver in the conventional way.

Vacuum corrections were applied. In the following table two analyses believed by the authors to have been made with defective material are omitted.

Atomic Weight of Copper.

Wt. of CuCl in vacuum.	Wt. of Ag in vacuum.	CuCl : Ag.	At. wt. of Cu.	Wt. of AgCl in vacuum.	CuCl : AgCl.	At. wt. of Cu.
5-62293	6-12732	0-917682	63-542	8-14097	0-690695	63-545
5-27787	5-75129	0-917685	63-543	7-64158	0-690678	63-543
6-08707	6-63310	0-917681	63-542	8-81308	0-690686	63-544
4-84195	5-27638	0-917665	63-541	7-01062	0-690659	63-540
5-93141	6-46362	0-917661	63-540	8-58810	0-690655	63-539
5-74879	6-26480	0-917663	63-541	8-32345	0-690674	63-542
5-83204	6-35517	0-917684	63-543	8-44382	0-690687	63-544
6-54858	7-13604	0-917677	63-542	9-48162	0-690660	63-540
6-21862	6-77653	0-917670	63-541	9-00373	0-690672	63-542
6-03859	6-58024	0-917685	63-543	8-74323	0-690659	63-540
Average		0-917675	63-542	—	0-690673	63-542

* 39-096, Baxter and Alter, *J. Amer. Chem. Soc.*, 1933, **55**, 3270; 30-096, Hönigschmid and Sachtleben, *Z. anorg. Chem.*, 1933, **213**, 365; 39-100, Johnson, *J. Physical Chem.*, 1935, **39**, 781; 39-098, Baxter and Harrington, *J. Amer. Chem. Soc.*, 1940, **62**, 1836; 39-096, McAlpine and Bird, *ibid.*, 1941, **63**, 2960.

The outcome of this work, 63.542, is appreciably lower than that of Richards and his collaborators, 63.57, on which the International value has depended for some time, but is in close agreement with that obtained by Ruer (*Z. anorg. Chem.*, 1924, 187, 101), 63.54, by reduction of cupric oxide, and with a recent isotopic analysis of copper by Ewald (*Z. Physik*, 1944, 122, 487) which gives the value 63.53.

Selenium.—Hönigschmid and Görnhardt (*Naturwiss.*, 1944, 32, 68) prepared pure selenium oxychloride by distillation in high vacuum in a glass still and collected the product in sealed glass bulbs. Analysis by comparison with silver chloride gave 78.961, while determination of the silver chloride produced 78.963 for the atomic weight of selenium. This investigation confirms the present International value which depends on the earlier synthesis of silver selenide by Hönigschmid and Kapfenberger. The value calculated from the proportions of isotopes is 78.95 (Flügge and Mattauach, *Ber.*, 1943, 76, A, 1).

Ruthenium.—Ewald (*Z. Physik*, 1944, 122, 491) has determined the isotopic proportions of ruthenium to be as follows:

Isotopic weight	96	98	99	100	101	102	104
Per cent.	5.68	2.22	12.81	12.70	16.98	31.34	18.27

With the packing fraction -6.49×10^{-4} and the conversion factor 1.000275 the atomic weight is calculated to be 101.04. Although Gleu and Rehm (*Z. anorg. Chem.*, 1937, 235, 352) by analysis of the *purpureo*-chloride obtained the value 101.08, the uncertainties in their determination make it unwise to make any change in the Atomic Weight Table at the present time.

Silver, Bromine, and Potassium.—McAlpine and Bird (*J. Amer. Chem. Soc.*, 1941, 63, 2960), by quantitative decomposition of potassium bromate, have found the ratio of potassium bromide to oxygen, and by comparison of the resulting potassium bromide with silver have found the ratio of these two substances. The results furnish a direct determination of the molecular weight of potassium bromide and an indirect determination of the atomic weight of silver.

Silver and bromine were purified by methods standard in atomic weight work. Potassium bromate was prepared from high-grade potassium hydroxide and an excess of bromine. After the solution had been boiled to remove excess of bromine and possibly iodine, the bromate was many times recrystallised until essentially free from bromide and sodium.

After prolonged drying in a vacuum the salt was further dried at 85–90° in the special weighed quartz decomposition flask, which was provided with a quartz filter disc to prevent loss of solid material, in a dry air stream, and was weighed. Very slow decomposition in a dry air stream followed, at gradually increasing temperatures up to 550°, until constant weight was obtained. During the decomposition the outgoing air stream was passed through a weighed phosphorus pentoxide tube to absorb residual water in the potassium bromate. In preliminary experiments it was found that decomposition of the bromate was complete and that the resulting bromide was neutral.

In the following table the weight of potassium bromate has been corrected for the water content as determined in each experiment. Vacuum corrections have been applied.

The Molecular Weight of Potassium Bromate.

KBrO ₃ , g.	KBr, g.	Ratio, KBr : O ₃	Mol. wt. of KBr.	KBrO ₃ , g.	KBr, g.	Ratio, KBr : O ₃	Mol. wt. of KBr.
10.67696	7.60833	2.47939	119.011	10.69361	7.62021	2.47941	119.012
7.54279	5.37493	2.47937	119.010	10.36524	7.38620	2.47939	119.011
7.44818	5.30753	2.47940	119.011	9.76351	6.95738	2.47935	119.009
9.72572	6.93055	2.47947	119.015	9.78441 *	6.97233	2.47942	119.012
9.62010	6.85524	2.47942	119.012				
8.50007	6.06711	2.47941	119.012				
				Average		2.47940	119.011

* Corrected in private communication from the authors.

Further evidence that the potassium bromide resulting from the decomposition was normal and free from moisture was obtained by comparing this bromide with silver in the conventional way by the nephelometric method. Similar experiments were made with potassium bromide prepared from pure bromine and potassium oxalate, and fused in nitrogen. Weights are corrected for air buoyancy.

If the established ratio of bromine to silver, 0.740786, is assumed, the atomic weights of bromine and potassium referred to silver as 107.879 are 79.915 and 39.096, respectively. All three values are in excellent agreement with those in the Table.

The Atomic Weight of Silver (KBr = 119.011).

KBr, g.	Ag, g.	Ratio, KBr : Ag.	At. wt. of Ag.*	KBr, g.	Ag, g.	Ratio, KBr : Ag.	At. wt. of Ag.*
KBr from KBrO ₃ .							
5.37498	4.87217	1.103200	107.878	7.62092	6.90813	1.103181	107.880
5.30758	4.81110	1.103195	107.878	7.38622	6.69531	1.103193	107.879
6.93122	6.28281	1.103204	107.878	6.95738	6.30663	1.103185	107.879
6.85536	6.21410	1.103194	107.879	6.97265	6.32040	1.103197	107.878
6.05813	5.49155	1.103173	107.881	Average		1.103191	107.879

KBr from K₂C₂O₄.

5.08563	4.60984	1.103212	107.877	5.30793	4.81142	1.103194	107.879
4.94988	4.48694	1.103175	107.880	4.50218	4.08093	1.103224	107.876
5.64545	5.11714	1.103243 †	107.874	4.34549	3.93902	1.103191	107.879
5.38516	4.88142	1.103195	107.878	5.25160	4.76034	1.103199	107.878
5.92139	5.36755	1.103183	107.880	5.06778	4.59372	1.103197	107.878
4.62504	4.19245	1.103183	107.880	Average		1.103200	107.878

* Recalculated from authors' data.

† 1.103200 in the authors' paper.

Incidental to the investigation three syntheses of silver chloride from silver were made.

The Ratio of Silver to Silver Chloride.

Ag, g.	AgCl, g.	Ag : AgCl.	Ag, g.	AgCl, g.	Ag : AgCl
6.95254	9.23774	0.752623	6.63263	8.81249	0.752640
7.03045	9.34116	0.752631	Average		0.752631

The previously established value of this ratio is 0.752632.

Silver.—Paul (*Naturwiss.*, 1943, 31, 419) has determined the proportions of the two isotopes of silver electrometrically with a mass spectroscope. The mean ratio from twelve determinations was found to be $\frac{^{107}\text{Ag}}{^{109}\text{Ag}} = 1.080 \pm 0.006$. If the packing fraction -4.8×10^{-4} is used the atomic weight of silver is found to be 107.880.

Dysprosium.—Wahl (*Suomen Kem. Tied.*, 1942, 51, 64; *Chem. Abstracts*, 1944, 38, 5142) finds the following isotopic proportions for dysprosium.

Isotope	158	160	161	162	163	164
Per cent.	trace	0.1	21.1	26.6	24.8	27.3

The mean mass number calculated from these percentages is 162.581, and with the packing fraction -1.3×10^{-4} and the conversion factor 1.000275 the atomic weight may be calculated to be 162.52. Owing apparently to the fact that the author's percentages total only 99.9, he calculates the incorrect value 162.42. Hönigschmid found, by analysis of the chloride, 162.46.

Hafnium.—Mattauch and Ewald (*Z. Physik*, 1944, 122, 314) by photometric measurement of intensities in mass spectrographic plates have found the relative abundances of the hafnium isotopes to be as follows :

Isotope	174	176	177	178	179	180
Per cent.	0.18	5.30	18.47	27.10	13.84	35.11

The mean mass number calculated from these results is 178.54, and the atomic weight calculated with the packing fraction $+0.2 \times 10^{-4}$ and the conversion factor 1.000275 is 178.50 ± 0.01 . This result is appreciably lower than the atomic weight found by Hönigschmid and Zintl (*Ber.*, 1925, 58, 453) in the usual chemical way. With two samples containing 0.57 and 0.16% of zirconium Hönigschmid and Zintl's results after correction for the zirconium content were 178.64 and 178.57.

Lead.—Permyakov (*Bull. Acad. Sci. U.R.R.S., Classe sci. chim.*, 1941, 581) has determined the atomic weight of lead from both Sadon galena and Khito-Ostrov uraninite by the conventional chloride-silver-silver chloride method. Weights are corrected to the vacuum standard.

Sadon galena.

Wt. of PbCl ₂ .	Wt. of Ag.	Ratio PbCl ₂ : 2Ag.	At. wt. of Pb.	Wt. of AgCl.	Ratio PbCl ₂ : 2AgCl.	At. wt. of Pb.
3.9615	3.0733	1.28900	207.20	4.0835	0.97010	207.19
2.2722	1.7628	1.28897	207.19	3.3423	0.97008	207.19
3.1425	2.4378	1.28907	207.21	3.2394	0.97009	207.19
Average		1.28901	207.20	—	0.97009	207.19

Khito-Ostrov uraninite.

1.6509	1.2928	1.28396	206.11	1.7175	0.96646	206.14
2.3032	1.7939	1.28391	206.10	2.3834	0.96635	206.12
2.2354	1.7411	1.28390	206.10	2.3132	0.96637	206.12
Average		1.28392	206.10	—	0.96639	206.13

Radium.—Attention is again called to the fact that in the most recent and accurate determination of the atomic weight of radium, by Hönigschmid and Sachtleben (*Z. anorg. Chem.*, 1934, 221, 85), by conversion of radium bromide into radium chloride, no correction was made for the fact that weights of salt are too low since the temperature of the salts is always higher than that of the balance. The ratio involved is $\text{RaBr}_2 : \text{RaBr}_2 - \text{RaCl}_2$, in which the second term is far less affected than the first. In earlier work by Hönigschmid a positive correction of 0.01 unit was used. Although the mass spectrographic value is 226.05, identical with Hönigschmid and Sachtleben's uncorrected result, the application of the above rather uncertain correction produces a discrepancy of 0.01 unit.

INTERNATIONAL ATOMIC WEIGHTS, 1947.

	Symbol.	Atomic Number.	Atomic Weight.		Symbol.	Atomic Number.	Atomic Weight.
Aluminium	Al	13	26.97	Neon	Ne	10	20.183
Antimony	Sb	51	121.76	Nickel	Ni	28	58.69
Argon	A	18	39.944	Niobium (Colum- bium)	Nb	41	92.91
Arsenic	As	33	74.91	Nitrogen	N	7	14.008
Barium	Ba	56	137.36	Osmium	Os	76	190.2
Beryllium	Be	4	9.02	Oxygen	O	8	16.0000
Bismuth	Bi	83	209.00	Palladium	Pd	46	106.7
Boron	B	5	10.82	Phosphorus	P	15	30.98
Bromine	Br	35	79.916	Platinum	Pt	78	195.23
Cadmium	Cd	48	112.41	Potassium	K	19	39.096
Cæsium	Cs	55	132.91	Praseodymium ...	Pr	59	140.92
Calcium	Ca	20	40.08	Protoactinium ...	Pa	91	231
Carbon	C	6	12.010	Radium	Ra	88	226.05
Cerium	Ce	58	140.13	Radon	Rn	86	222
Chlorine	Cl	17	35.457	Rhenium	Re	75	186.31
Chromium	Cr	24	52.01	Rhodium	Rh	45	102.91
Cobalt	Co	27	58.94	Rubidium	Rb	37	85.48
Copper	Cu	29	63.54	Ruthenium	Ru	44	101.7
Dysprosium	Dy	66	162.46	Samarium	Sm	62	150.43
Erbium	Er	68	167.2	Scandium	Sc	21	45.10
Europium	Eu	63	152.0	Selenium	Se	34	78.96
Fluorine	F	9	19.00	Silicon	Si	14	28.06
Gadolinium	Gd	64	156.9	Silver	Ag	47	107.880
Gallium	Ga	31	69.72	Sodium	Na	11	22.997
Germanium	Ge	32	72.60	Strontium	Sr	38	87.63
Gold	Au	79	197.2	Sulphur	S	16	32.066
Hafnium	Hf	72	178.6	Tantalum	Ta	73	180.88
Helium	He	2	4.003	Tellurium	Te	52	127.61
Holmium	Ho	67	164.94	Terbium	Tb	65	159.2
Hydrogen	H	1	1.0080	Thallium	Tl	81	204.39
Indium	In	49	114.76	Thorium	Th	90	232.12
Iodine	I	53	126.92	Thulium	Tm	69	169.4
Iridium	Ir	77	193.1	Tin	Sn	50	118.70
Iron	Fe	26	55.85	Titanium	Ti	22	47.90
Krypton	Kr	36	83.7	Tungsten	W	74	183.92
Lanthanum	La	57	138.92	Uranium	U	92	238.07
Lead	Pb	82	207.21	Vanadium	V	23	50.95
Lithium	Li	3	6.940	Xenon	Xe	54	131.3
Lutecium	Lu	71	174.99	Ytterbium	Yb	70	173.04
Magnesium	Mg	12	24.32	Yttrium	Y	39	88.92
Manganese	Mn	25	54.93	Zinc	Zn	30	65.38
Mercury	Hg	80	200.61	Zirconium	Zr	40	91.22
Molybdenum	Mo	42	95.95				
Neodymium	Nd	60	144.27				

OBITUARY NOTICE.

ARTHUR LAPWORTH.

1872—1941.

ARTHUR LAPWORTH was born on October 10th, 1872, at Galashiels; his father was Charles Lapworth (F.R.S., 1888, Royal Medallist, 1891), the eminent first Professor of Geology in the University of Birmingham, who was a pioneer in laying the foundations of stratigraphy. After early education at St. Andrews and at King Edward's School, Birmingham, he graduated at Mason College and, as an 1851 Exhibitioner (1893—95), proceeded to the City and Guilds of London Institute, where the presiding genius was H. E. Armstrong. However, Lapworth came more directly under the care of F. S. Kipping, who was at that time in charge of the main organic laboratory.

Professor Kipping writes :

" From the very first it was obvious that Lapworth had the experimental skill, as well as the powers of acute observation and sound deduction which would ensure his success in scientific work, and that his vivid imagination and high intellect would take him far in his profession. Any one who made Lapworth's acquaintance could not fail to wish for closer ties, and although he was considerably my junior in age we soon became fast friends; perhaps it would be truer to say that our relationship, even in those early days, was rather that of congenial brothers. He became a frequent visitor at our house in South Kensington, where he often met Pope, Forster, and other workers in Armstrong's laboratories, and my wife soon shared with me the great pleasure of his friendship. During one vacation when he had made no holiday plans, we asked him to stay with us at Bridgwater: here it was that he met his future wife, Kathleen Holland, with whom during forty years he spent the rest of his life in peaceful and loving marital harmony."

To this may be added that Kathleen was the younger sister of Mrs. Kipping and of Mrs. W. H. Perkin; thus Mrs. Holland was the mother-in-law of three distinguished chemists and Fellows of the Royal Society.

His postgraduate course at the " Central " included crystallography under the late Sir Henry Miers and following this he worked with Armstrong on the sulphonation of ethers of β -naphthol and with Kipping on derivatives of camphor and camphene. So began two of his main interests in later research, the chemistry of camphor and the mechanism of aromatic substitution. His D.Sc. thesis,* submitted at the age of twenty-three, on the naphthalene topic was the occasion for a characteristic display of courageous independence. He refused to alter some sections of the theoretical treatment which his formidable professor had criticised.

Lapworth's first post (1895) was that of Demonstrator in Collie's laboratory at the School of Pharmacy in Bloomsbury. One joint paper (*J.*, 1897, **71**, 838) on picoline derivatives from this period bears the Collie stamp. In 1900 he went to the Goldsmiths' Company's Institute at New Cross as Head of the Chemistry Department (1906, Goldsmiths' College) and in 1909 became Senior Lecturer in Inorganic and Physical Chemistry and Schunck Fellow at the University of Manchester. Four years later he succeeded W. H. Perkin, jun., in the Chair of Organic Chemistry and in 1922 became Sir Samuel Hall Professor (primarily responsible for physical and inorganic chemistry) and Director of the Laboratories. The writer, first as a Junior Demonstrator and, after an interval of years, as Professor of Organic Chemistry, had the inestimable privilege of his friendship and collaboration. At lunch in the refectory and at many other times we exchanged ideas, often expressed on the back of envelopes by what Armstrong was pleased to call " noughts and crosses ". During this latter period Mrs. Lapworth acted as his secretary in the department.

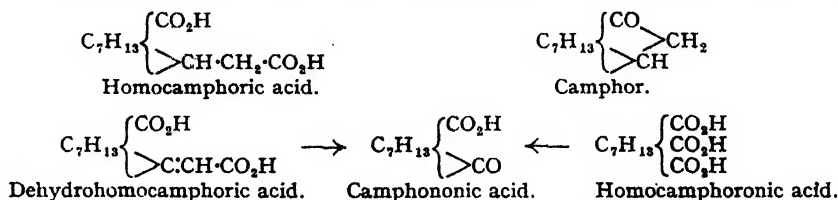
His last appointment demonstrates Lapworth's remarkable breadth and versatility; very few men in the twentieth century would be thought competent to hold in succession chairs of organic and physical chemistry. He retired in 1935 and was appointed Professor Emeritus. He was elected F.R.S. in 1910, served on the Council (1927—29), received the Davy Medal in 1931, and was an honorary LL.D. of Birmingham and of St. Andrews universities. These distinctions are mentioned with some uneasiness; high as they are they afford no measure of the achievement of a man whose influence on chemical philosophy was outstanding.

His modest disposition did not bring him into the limelight; he was not a showman, tending rather to disparage his wares; he made no dramatic discoveries such as to catch the public eye;

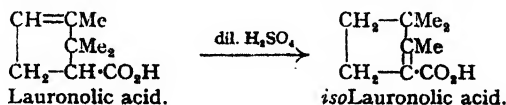
* " Sulphonic acids of betamethoxy- and betaethoxy-naphthalene." Thesis for D.Sc. (London), April, 1895.

he never flogged a dead horse and even left some promising live ones to fend for themselves. He investigated in order to learn something, to educate himself, and not with the primary object of producing elegant and finished scientific memoirs, though he did indeed leave many such on record. Much of his work seems, therefore, incomplete, and his output of over a hundred papers was, judged by some standards, relatively small. Yet the power of his genius triumphed and it is now possible to see how his ideas, always many years ahead of those of his contemporaries, played a leading part in the contribution which organic chemists have made to the revolution in chemical thought. The electronic theory of valency has made it possible to give a measure of precision to many of the suggestions he advanced on an electrochemical basis, but Lapworth's preparation of the ground was essential. During many years little attention was paid to his views; now they are the commonplaces of the textbooks.

One of Lapworth's first major interests was the constitution of camphor and the way he attacked the problem was very significant. There are quite a number of ordinary papers on the detailed chemistry of derivatives; just the kind of thing that many workers in the field could, and did, produce. Certainly some of this material was of great importance and demonstrated his skill as an experimentalist, in particular his study of homocamphoric acid (*J.*, 1899, 75, 986; 1900, 77, 446, 1053) forged a vital link in the chain of evidence. In this investigation he showed that homocamphoric acid can be degraded to dehydrohomocamphoric acid and then to camphononic acid, which must be a *cyclopentane* derivative because it could be synthesised by ketonisation of homocamphoronic acid. But his characteristic contribution was an idea—an

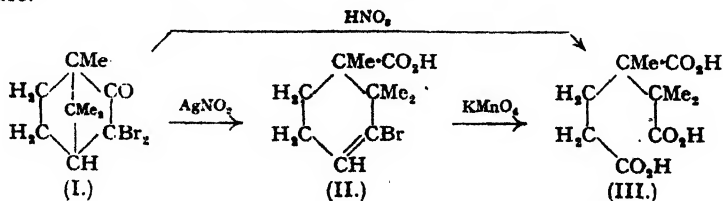


interpretation of the chemistry of camphor which reconciled apparently conflicting data (*Brit. Assoc. Rep.*, Sec. B, Bradford, 1900). In other words he saw through the mist and by recognising the occurrence of a remarkable molecular rearrangement in the formation of *isolaunonic* acid removed the chief stumbling block to the general acceptance of *Bredt's* camphor formula.



The postulated intramolecular change was compared by Lapworth with the pinacol-pinacolone rearrangement and a similar explanation was also applied to the change of α - to β -campholenic acid, which was another source of confusion.

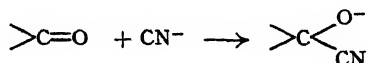
Homocamphoronic acid (III) itself and the stages of its production from $\alpha\alpha$ -dibromocamphor (I) gave a great deal of trouble, as may well be understood when the direct formation of the acid by oxidation of (I) with nitric acid is considered (*J.*, 1899, 75, 986). A carbon atom seems to get out of place.



It was shown, however, that Forster's bromocamphorenic acid (II) is probably an intermediate product, and the very remarkable molecular rearrangement, (I) \longrightarrow (II), was suggested as the result of an extensive series of investigations (*J.*, 1899, 75, 1134; 1900, 77, 309, 446; 1902, 81, 17). Lapworth carried these out in a systematic fashion by the careful study of the properties and reactions of the substances mentioned and, in addition, of camphonic acid, camphononic acid, and various bromo-lactones. It does not seem to have occurred to him to

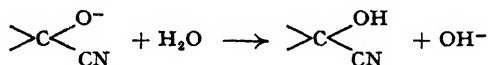
attempt the synthesis of homocamphoronic acid, although that is perhaps due to the fact that the structures became clear only towards the end of a prolonged study.

The examples cited of the mobility of the camphor complex could be supplemented by many others and there is no doubt that the general acceptance of Bredt's formula owed as much to Lapworth's searching analysis as to the eventual synthesis of camphoric acid. Much later he prepared homocamphor (*J.*, 1920, 117, 743), but the connecting link with later activities was perhaps his work on cyanocamphor and homocamphoric acid (*J.*, 1900, 77, 1053). He was led to consider the problem of the addition of hydrocyanic acid to carbon compounds more generally and especially to the $\alpha\beta$ -unsaturated ketones and the ketones and aldehydes themselves (*J.*, 1903, 83, 995; *Proc.*, 1904, 20, 245; *J.*, 1904, 85, 1206—1214, 1355; 1906, 89, 1819, 1869; 1907, 91, 694, 977; 1910, 97, 11; *Proc.*, 1911, 27, 240; *J.*, 1911, 99, 1877; 1928, 2533; 1930, 1976). The studies ranged from observations of the β -addition of cyano-groups to $\alpha\beta$ -unsaturated ketones such as mesityl oxide, benzylideneacetone, carvone, and pulegone to the later, careful examination of the conditions of formation and the stability of cyanohydrins. There is little doubt that reflection on the mechanism of these reactions played an important part in directing his attention to the principle of "alternate polarities". From the first he adopted ionic mechanisms, and a good illustration of his ideas is seen in the view he put forward of the course of the formation of benzoin from benzaldehyde (*J.*, 1907, 91, 694). The production of a cyanohydrin was regarded by Lapworth as involving the direct attack of cyanidion on a carbonyl group:



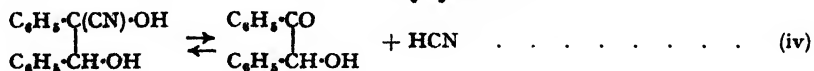
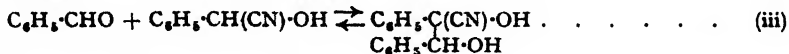
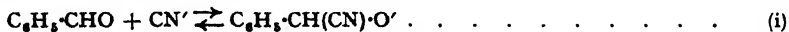
This he made very probable by a study of the effect of catalytic agents on the velocity of the addition (*J.*, 1903, 83, 995) and by showing that the cyanohydrins are complex acids of which he was able to prepare the salts (*J.*, 1904, 85, 1206). Thus by the action of potassium cyanide on benzaldehyde and camphorquinone he obtained crystalline potassium salts of the cyanohydrins. This view was confirmed by much subsequent research by Lapworth himself, by Bredt, and by Goldschmidt.

The second stage in the formation of a cyanohydrin is the decomposition of water, or an alcohol or acid, by the complex ion:



He early recognised that these processes must be reversible and that normally an equilibrium will be set up. The theory explained very well why cyanohydrins are so advantageously prepared by the action of pure hydrocyanic acid on a ketone in the (necessary) presence of a small proportion of an alkaline catalyst, which may be potassium cyanide, or may even be derived from the glass container.

To complete the scheme of the benzoin synthesis it was assumed that benzaldehyde undergoes an aldol-like synthesis with mandelonitrile, and that the cyanohydrin of benzoin is relatively unstable. This was probable on theoretical grounds, and from analogies, but it was also experimentally demonstrated. The complete scheme was (*J.*, 1907, 91, 694):

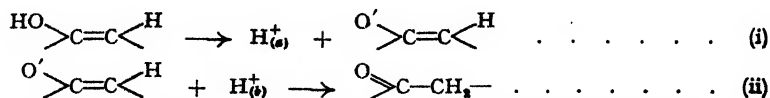


It will be noticed that Lapworth postulated reversibility of each stage. The theory has stood the test of forty years and is generally accepted as correct: undoubtedly it represented a landmark in the progress of our understanding of the course of chemical change.

Another outcome of the early camphor period was the use made of optical activity to study the phenomena of desmotropic, or tautomeric, change (*J.*, 1902, 81, 1491, 1499, 1508; 1903, 83, 114; 1904, 85, 46; 1911, 99, 1785). From the first Lapworth regarded these processes from the ionic point of view first advanced by Brühl in 1899, but in a less explicit form. He, however,

greatly extended the conception and supported it by many experimental researches carried on throughout his active career.

Mechanisms were invariably adopted which stressed the fact that the ions, particularly hydrogen ions, must often be regarded as coming in from outside and also as leaving for an unknown, and possibly remote, destination. Thus in keto-enol tautomerism catalysed by acids we have :



where the two protons *a* and *b* are not the same. Although these views, and perhaps some others that he advocated, were not completely novel, Lapworth made a better combination of them than any other chemist. His consistency and theoretical insight made a great impression on his contemporaries and exercised a powerful influence on the development of organic chemical theory. At a later stage he became interested in the mechanism of esterification and hydrolysis (*Proc.*, 1908, 24, 100, 152, 153; *J.*, 1908, 93, 2163, 2187; *Proc.*, 1909, 25, 20; *J.*, 1910, 97, 19; 1911, 99, 917, 1417, 1427, 2242; 1912, 101, 2249; 1913, 103, 252; *Proc.*, 1914, 30, 141; *J.*, 1915, 107, 857; 1922, 121, 76). Here again the emphasis was on hydrogen ion catalysis and the theory of acids and complex ions in various media. The researches were developed with the refinements of physico-chemical techniques and cannot usefully be summarised in the course of a short discussion. Many aspects of the work were unfinished and inconclusive but, taken as a whole, it must be admitted that this series of memoirs made an essential contribution to a subject which has excited great interest, and has of course been advanced by many other workers.

Another penetrating suggestion made by Lapworth concerned the mechanism of the bromination of ketones; the case chosen for study was acetone. The rate of bromination was found to be independent of the concentration of bromine and the process was catalysed by acids.

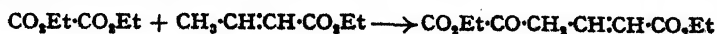
Lapworth suggested that the rate-determining change is the formation of enol from the acetone and that this is immediately brominated. The reaction is therefore autocatalytic due to the accumulation of hydrogen bromide. This view is accepted to-day for the acid-catalysed reaction, but other ions than hydrogen ions play a part and the complexity of the system is illustrated by H. M. Dawson's subsequent examination of the iodination of acetone. Anionotropic as well as prototropic reactions are in evidence. Considering the date (1913) of Lapworth's work (*Proc.*, 1913, 29, 283) the advance he made was remarkable.

The conception of very rapid bromination of an enol was later utilised by K. H. Meyer for the analysis of mixtures of enols and ketones, for example, ethyl acetoacetate, under various circumstances. Lapworth often told the writer that he ought to have made this ingenious but obvious application. It is, however, doubtful whether full enolisation occurs, and it is not necessary to postulate it. Thus Leuchs has shown that an optically active ketone, the enol of which must be optically inactive, can be brominated without loss of activity. This recalls the observation of Kuhn and Albrecht that optically active *sec.*-nitrobutane yields an optically active sodium salt. Many other examples of Lapworth's concern with reaction mechanisms could be cited, including his early generalisations of the form of intramolecular changes (*Proc.*, 1895, 11, 49; *J.*, 1898, 73, 445; *Proc.*, 1901, 17, 2; *J.*, 1901, 79, 1265) and an examination of the synthesis of acetoacetic ester (*Proc.*, 1903, 19, 189). Moreover he made kinetic studies of many reactions other than those mentioned and his work on the rate of oximation and the properties of oximes (*J.*, 1902, 81, 549; 1907, 91, 1133; 1908, 93, 85) may be given in illustration.

Lapworth discovered many new reactions and transformations of which the following are among the more interesting.

Possibly his investigations of the addition of hydrogen cyanide to unsaturated ketones suggested that the quality of reactivity of the carbon of a carbonyl group can be transmitted to the β -carbon of an $\alpha\beta$ -unsaturated ketone. If so, he may have argued, a carbonyl might activate a methylene group through a double bond. At any rate, in 1900 he made an experiment that must have had some such theoretical background.

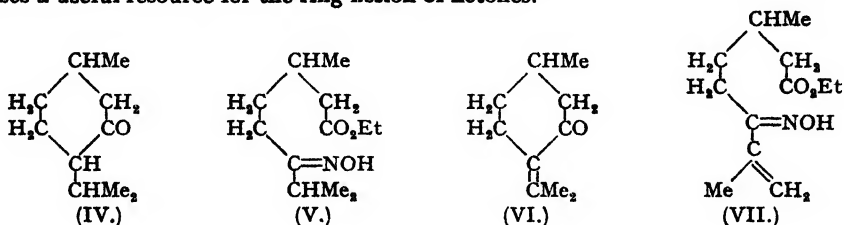
He found (*Proc.*, 1900, 16, 132) that ethyl crotonate condensed with ethyl oxalate in the presence of sodium ethoxide as follows :



The constitution of the product has since been confirmed; this was necessary in view of the possibility of the double bond migration to the $\beta\gamma$ -position, followed by oxylation in the α -position. An extension was made later (*J.*, 1923, 123, 1325).

Lapworth and Wechsler (*J.*, 1907, 91, 1919) noted an anomalous reaction of cyanodihydrocarvone with amyl nitrite in the presence of sodium ethoxide. Further experiments revealed an interesting scission of ketones containing the group —CO—CH— under the same conditions. It may be assumed that a nitroso-derivative is first formed and that this adds the elements of alcohol to yield $\text{—CO·OEt} + \text{HON·C<}$ (*J.*, 1908, 93, 30).

Thus menthone (IV) yields (V) after hydrolysis of the product; pulegone (VI) gives (VII), the process involving the above-mentioned shift of a double bond. A simple model was provided (*J.*, 1911, 99, 1882) by phenyl isopropyl ketone, Ph·CO·CHMe_2 , which was found to be converted by amyl nitrite in alcoholic sodium ethoxide into benzoic ester, $\text{Ph·CO}_2\text{Et}$, and acetoxime, HON=CMe_2 . This reaction has been applied to cinchoninone and affords in this and other cases a useful resource for the ring-fission of ketones.



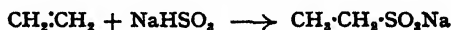
Another degradation was discovered when bromine was allowed to act on ethyl benzeneazooacetate, $\text{CH}_3\text{·CO·CH(N}_2\text{Ph)·CO}_2\text{Et}$, when the acetyl group was eliminated and a so-called hydrazino-derivative, $\text{CBr(N·NHPh)·CO}_2\text{Et}$, was produced (*J.*, 1905, 87, 1854). When treated with alkalis, two molecules condensed to give ethyl diphenyldihydrotetrazinedicarboxylate,



These novel types of substances have not received much subsequent attention.

An interesting paper on sulphonic esters (*J.*, 1912, 101, 273) describes some new reactions based on the idea that esters and sulphonic esters tend to undergo scission at the dotted line:

$\text{R·CO·}\ddot{\text{O}}\text{—R'}$, $\text{R·SO}_2\text{·}\ddot{\text{O}}\text{—R'}$. It was found that olefins add the elements of sulphurous acid with the production of sulphonic acids (*J.*, 1925, 127, 307). In the simplest case ethylene reacts with sodium hydrogen sulphite with formation of ethanesulphonic acid, which was isolated as the barium salt:



This reaction was rather unexpected; it underlines the abnormality of sulphur and recalls Posner's experiments on the addition of mercaptans to unsaturated substances.

At various times Lapworth paid considerable attention to improvements of preparative methods and to the prescription of satisfactory recipes. For example, he made really pure oleic acid (*Biochem. J.*, 1925, 19, 7) and studied its quantitative oxidation to dihydroxystearic acid (*J.*, 1925, 127, 1628, 1987). This is only one instance of his interest in the chemistry of the fats. He began work on sphingosine and cerebrone (*J.*, 1913, 103, 1029) but never carried it far.

Other illustrations of the improvement of methods are the reductions of emulsified nitro-compounds (*J.*, 1921, 119, 765, 768; 1925, 127, 2970) whereby excellent yields of arylhydroxylamines were obtained, and contributions to *Organic Syntheses* (1927, 7, 20; 1928, 8, 99) based on his earlier work with McRae (*J.*, 1922, 121, 1699, 2741). The details are characteristically elegant. An aldehyde such as benzaldehyde is brought into reaction with sodium cyanoacetate, previously made in the usual way; the addition of hydrocyanic acid and hydrolysis then afford a substituted succinic acid.

An unusual development for Lapworth was a study of natural products, in this case the pungent principles of ginger (*J.*, 1917, 111, 77) and capsicum (*J.*, 1919, 115, 1109). It is curious that E. K. Nelson, and also H. Nomura, published work on gingerol almost simultaneously with that of Lapworth, Pearson, and Royle. The work of Lapworth and his collaborators was the most comprehensive. The oleo-resin of Thresh, and of Garnett and Grier, methylated by means of methyl sulphate and alkali, yields a crystalline compound termed methylgingerol. This is decomposed by heat or alkali into methylzingerone, $\text{C}_{15}\text{H}_{16}\text{O}_2$, and aldehydes, of which the chief is *n*-heptaldehyde. Methylzingerone was proved by analysis and synthesis (*J.*, 1917,

was seen to be divergence, however, in other important respects and the origin of these became clear with the development of translations into the terms of the electronic theory of valency.

The working hypothesis of "labelling" from a key-atom gave rise to some interesting experimental work and an early example is that of Lapworth and Shoesmith (*J.*, 1922, 121, 1391) on the methoxybenzyl bromides.

Thus the *m*- and *p*-isomerides are labelled from oxygen as key-atom :



The behaviour of these substances was found to harmonise with that predicted from the figures. It was known that Br in, for example, $\text{O}=\text{C}^+-\text{Br}^-$ is very readily replaced by OH and that Br in $\text{O}=\text{C}^+-\text{CH}^+-\text{Br}^-$ is unusually readily replaced by H. *p*-Methoxybenzyl bromide was much more easily hydrolysed to the related alcohol than was *m*-methoxybenzyl bromide, and in reductions to the tolyl methyl ethers, the *m*-isomeride was the more reactive.

Nowadays the properties of the *p*-derivative can be readily interpreted on a more precise electronic basis, but the *m*-derivative would be regarded as a benzyl bromide, lacking the special constitutive features of the *p*-type, and differing from benzyl bromide itself only as the result of the general electrical effect of the methoxy-group. In other words, it is the *p*-derivative that exhibits exceptional behaviour, and a comparison of benzyl bromide and *m*-methoxybenzyl bromide is required in order to estimate the significance of the contrast to which Lapworth and Shoesmith drew attention.

About this period (1922—26) an active controversy arose (cf. *J.*, 1925, 127, 1742); this consumed much time and effort but need not be described in detail. Lapworth himself would be the last to desire these ephemeral writings to be resuscitated on account of their purely historical interest. It had at least one useful result in that the theory was more quickly moulded into its present form.

The chief subsequent events have arisen from the applications of quantum mechanics to organic chemical problems. These have provided a new calculus for the electronic theory of valency but have not rendered the older qualitative approach obsolete.

Lapworth's last scientific paper (*J.*, 1931, 1959) was most happily a collaborative effort with Professor C. K. Ingold. It was concerned with the problem of *m*-nitration of toluene. Competitive nitrations of toluene and benzene show that toluene is far more readily attacked than benzene. But in the nitration of toluene, only 4.4% of the *m*-derivative is produced. The question arises—does the methyl group activate the *m*-position, relative to the reactivity of benzene? Careful experiments showed that this is indeed the case, the disparity of toluene and benzene reactivity being sufficient.

There is little doubt that Lapworth would have continued to shed light on these and similar problems but unfortunately signs of his illness made their appearance early in the third decade of the century. He continued for some years to inspire his colleagues and collaborators by discussion and correspondence. Indeed it is true to say that throughout his life, though his publications are highly important, his generous help to others had an almost equal, if not greater, influence on the progress of science.

The world-wide recognition of Lapworth's genius and his abiding scientific reputation increases with the passage of time. It is now seen that his insight into chemical mechanisms, and his insistence on the electrochemical point of view at the molecular level, forged a necessary link in the chain of theory which now connects the most diverse phenomena.

In the laboratory one of his students, Dr. G. N. Burkhardt, gives the following picture. "He was skilful in devising and using the simple methods which he always preferred and, with a home-made cigarette in one corner of his mouth, and his head on one side, he would attack a new substance with reagents and a set of test-tubes. Using traces of material and a number of uncommon devices, he would find as much in a few minutes as might take hours to establish on a larger scale with more elaborate technique. As a teacher, lecturing on three main branches of chemistry in succession, he concerned himself to an unusual degree with the exposition of ideas, methods, and general principles, so that his lectures were most stimulating and valuable to his

better students, though they could be the despair of those whose tastes or abilities required only the easy catalogue of facts."

In his dealings with his fellow men he was selfless, generous to a fault, and completely straightforward and sincere. His scientific work occasionally brought him into controversy with exponents of older views, but this was always conducted with great dignity and the most careful choice of words. Incidentally he possessed an enviable command of language especially noticed in his writing, and a pretty and sometimes caustic wit, entirely free from any suspicion of malice. As administrator of his department and laboratory he showed firmness and wisdom, but this was not his real *métier* and it is a pity that a sense of duty compelled him to undertake responsibilities which turned out to last far too long. As already mentioned, the valuable help of Mrs. Lapworth lightened the load of routine for several years. The loyalty with which Lapworth was served and the undying devotion of all those who collaborated with him whether in teaching or research are the best testimony to his professional work and the University of Manchester owes much to his encouragement of young men of promise and to his guidance of the School of Chemistry during critical years.

A sensitive soul, always sparkling with vitality, all-embracing in his curiosity and interest, it is natural that he had many hobbies.

His father was a pianist and his mother and sister were accomplished singers. He himself played the violin and 'cello and was a lover of music, with sound and individual taste and a wide knowledge of the classics. He had little use for the modern forms. At New Cross he took part, as violinist, in chamber music and played in the College orchestra. When he came to Manchester Perkin asked him to share in his famous musical parties but there were too many violinists and Lapworth learned the viola. For many years he served on the Council of the Royal Manchester College of Music. He was a good dancer, was fond of the theatre, of films, radio, and the gramophone, and, in my time, he was a voracious reader of thrillers. Carpentry and microscopy were just two of his pursuits, and outside his chemistry his main scientific interests were astronomy, geology, and botany. He was an authority on British mosses and made a fine collection of them.

Holidays were spent in mountaineering and later in golfing and fishing. As a boy he started scrambling at St. Andrews and soon accompanied his father on geological expeditions to the mountains. At the age of eighteen he made a solitary ascent of the Petit Dent de Veisivi and later climbed Lliwedd and the Rosenlauri Engelhörner by several routes.

Much affected by the loss of his friend Humphrey Owen Jones and his wife on the Aiguille Blanche de Peteret, he never climbed again.

His fishing ground was chiefly the river Eden near Gosforth, and he was a member of the Yorkshire Anglers Club. Speaking of one of his friends he said: "The keenest angler I know—what a pity that he never catches fish".

The outdoor life consorted well with his interest in nature, and it was K. J. P. Orton who introduced him to the study of birds. Orton, a recognised authority, was good with the field-glasses, but Lapworth's trained and sensitive ear enabled him to surpass his teacher in the recognition of birds by song. Birding with the Ortons was the *raison d'être* of many happy expeditions round Hayes Common, Keston, and in the Bangor district. Many years later the writer found in a St. Andrews "den" that Lapworth had not forgotten his craft.

The breadth of interest and joy in life which Lapworth showed in his recreations were characteristic of the man. In science, too, his temperament might have caused too wide a spread, but he was saved from this by self-discipline and by a dominant theoretical theme.

Lapworth's health, at least in later years, was never robust, and the exceptional strain of carrying the burden of the whole Department of Chemistry eventually broke it down. His long and distressing illness was borne with the greatest fortitude, but, until the very end, he never lost his interest and was able to enjoy the visits of his friends at intervals.

R. ROBINSON.

186. Photochemical Reactions in Sunlight. Part XII. Reactions with Phenanthraquinone, 9-Arylxanthenes, and Diphenyl Triketone.

By ALEXANDER SCHÖNBERG and AHMED MUSTAFA.

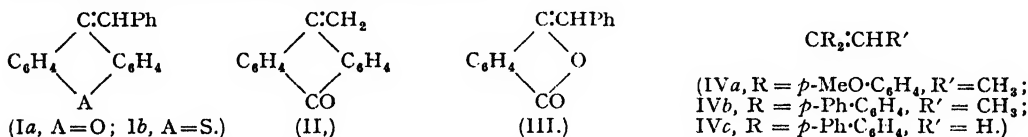
(a) The photochemical addition of phenanthraquinone or retenequinone to various substances containing an olefinic linkage has been carried out. The olefinic compounds include diphenylketen and a number of olefins, (I)–(III), in which one carbon atom of the ethylenic linkage is a member of a five- or six-membered ring system. The photo-products obtained are represented by the formulæ (V)–(VIII).

(b) Reaction scheme (A), which shows the photo-formation of peroxides from 9-arylxanthenes, was carried out in five cases. Some of the arylxanthenes are new and were prepared according to scheme (B). 9-Benzylxanthen was stable in sunlight in the presence of oxygen.

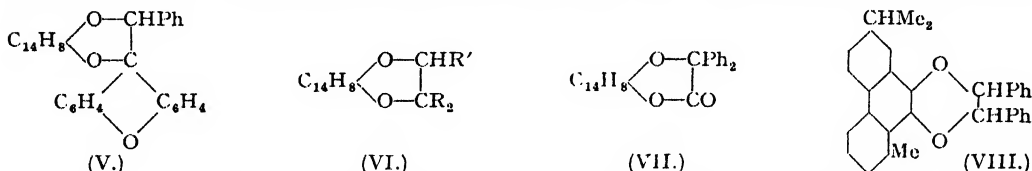
(c) The photo-reaction between phenanthraquinone and aromatic aldehydes was studied in three cases (see C); steric hindrance (ortho-effect) may explain the slow rate of the photo-reaction in the case of 2-methoxy-1-naphthaldehyde.

(d) Diphenyl triketone in sunlight forms benzil.

(a) RECENTLY (J., 1944, 387; 1945, 551) we showed that phenanthraquinone reacted with certain unsaturated compounds to form derivatives of phenanthro-1:4-dioxen. We have now extended this reaction to 9-benzylidene-xanthen and -thioxanthen (I, *a* and *b*), methyleneanthrone (II), benzylidenephthalide (III), 1:1-di-*p*-anisylpropylene (IV*a*), 1:1-dixenylpropylene (IV*b*), *as*-dixenylethylene (IV*c*), and diphenylketen.



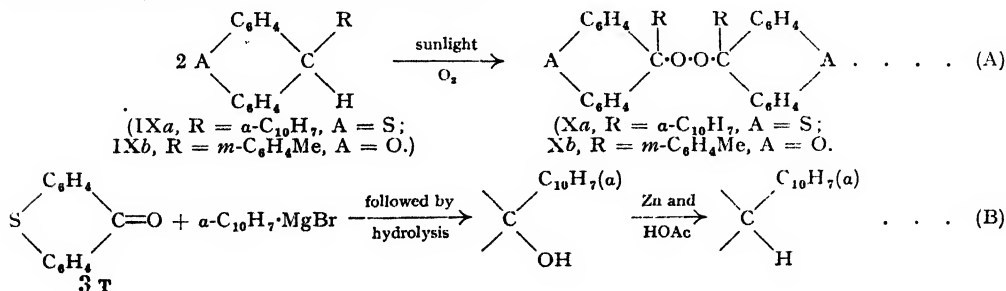
The photo-product obtained from (Ia) has the structure (V), and those from (Ib), (II), and (III) are analogous. Those from (IV, *a*, *b*, and *c*) are of type (VI), in which R and R' are as in the three formulæ. Diphenylketen gives the compound (VII). The condensation product from



retenequinone and stilbene is assigned the structure (VIII). All these products are colourless except (VIII), which is light yellow. On pyrolysis, the compounds were resolved into their generators except that diphenylketen was not obtained from (VII), probably because of its thermolability.

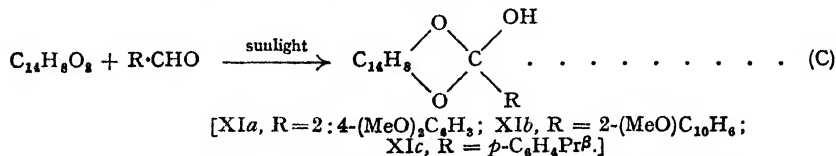
The photo-products from (III) and diphenylketen were insoluble in aqueous sodium hydroxide, but were readily attacked when heated with aqueous-alcoholic sodium hydroxide, a behaviour according with the lactone structure assigned to them; the resulting solutions were orange-coloured.

(b) To the list of triarylmethanes forming peroxides in air and sunlight by route (A) (Schönberg and Mustafa, J., 1945, 657), we now add 9-*α*-naphthylthioxanthen, 9-*m*-tolylxanthen, and 9-*p*-tolyl-, 9-*p*-anisyl-, and 9-*α*-naphthyl-xanthen. The first two are new and were prepared as shown in (B) for the naphthyl compound:



9-Benzylxanthen in benzene was unchanged when exposed to sunlight in presence of oxygen. It seems that an aryl group in position 9 in xanthyl is necessary for the formation of peroxides in sunlight by the action of oxygen.

(c) Schönberg and Moubasher (*J.*, 1939, 1430) described a number of photo-reactions between phenanthraquinone and aromatic aldehydes according to (C). We have carried out similar reactions with 2 : 4-dimethoxybenzaldehyde, 2-methoxy-1-naphthaldehyde, and cuminaldehyde; the first two reactions are much slower than that between benzaldehyde and phenanthraquinone in sunlight : this may be due to steric hindrance (ortho-effect).



(d) Lately, two methods have been described for conversion of diphenyl triketone into benzil by processes in the dark, namely, by the action (i) of aluminium chloride and (ii) of selenium (precipitated) in the presence of oxygen (Schönberg and Azzam, *J.*, 1939, 1430; Schönberg and Moubasher, in the press). It has now been found that the conversion is also effected when a benzene solution of the triketone is exposed to sunlight, but no reaction takes place in the dark in the absence of catalysts.

EXPERIMENTAL.

All substances were in solution unless otherwise stated. The benzene used was free from toluene* and thiophen and had been dried over sodium. The reaction mixtures were placed in a Schlenk tube (Schlenk and Thal, *Ber.*, 1913, 46, 2655; comp. Houben, "Die Methoden der Organischen Chemie", 2nd Edition, Vol. 4, p. 960) of Pyrex glass, and the air was then displaced by dry carbon dioxide and the tube sealed by fusion.

The photo-formation of peroxides was carried out as above, but in the presence of dry air.

Control experiments in the dark, but otherwise under identical conditions, showed no reaction.

(a, i) *Photo-reactions with Phenanthraquinone.*—9-Benzylidenexanthien. Phenanthraquinone (1 g.) and 9-benzylidenexanthien (Ia) (Decker, *Ber.*, 1905, 38, 2493) (1.3 g.) in benzene (50 c.c.) were exposed to sunlight for 4 months (February—June), the phenanthraquinone gradually dissolving completely. The benzene was evaporated off in a vacuum, and the residual dark solid washed with cold acetone and crystallised from benzene—light petroleum (b. p. 30—50°), forming almost colourless crystals, m. p. 241° (red brown melt) (Found : C, 84.8; H, 4.9. C₂₄H₂₂O₃ requires C, 85.3; H, 4.6%). The product (V), when treated with sulphuric acid, gave an olive-green colour; it was soluble in hot benzene and ligroin (b. p. 100—150°).

Thermal decomposition. The foregoing product was heated for ½ hour at about 270° (bath temp.) in a stream of dry carbon dioxide (the height of the decomposition tube being about 25 cm.); red-brown fumes were evolved, and an orange liquid collected on the walls of the tube. After 24 hours, this solidified to a mixture of orange and almost colourless crystals; extraction with hot light petroleum (b. p. 50—60°) left a residue of phenanthraquinone (identified, after recrystallisation from alcohol, by m. p., mixed m. p., and colour reaction with sulphuric acid). The extract was concentrated, and the resulting crystals, recrystallised from ethyl alcohol, proved to be 9-benzylidenexanthien (Ia).

9-Benzylidenethioxanthien. Phenanthraquinone (1 g.) and 9-benzylidenethioxanthien (Ib) (Decker, *loc. cit.*) (1.4 g.) in 30 c.c. of benzene were exposed to sunlight for 3 months (August—November), the phenanthraquinone dissolving as before and the orange colour of the solution fading to pale yellow. The crystals that separated were filtered off, washed several times with hot absolute ethyl alcohol, and recrystallised from benzene, forming colourless crystals, m. p. 245° (orange melt) (Found : C, 82.6; H, 4.6; S, 5.9. C₂₄H₂₂O₂S requires C, 82.6; H, 4.4; S, 6.5%). The product (as V) gave a brown colour with sulphuric acid at room temperature; it was difficultly soluble in cold ethyl alcohol, but soluble in hot benzene; when heated as described above, it yielded its generators, which were separated as above.

Methyleneanthrone. Phenanthraquinone (1 g.) and methyleneanthrone (II) (Clar, *Ber.*, 1936, 69, 1687) (1 g.) in 25 c.c. of benzene were exposed to sunlight for 40 days (February—April); the phenanthraquinone dissolved, and the resulting crystals were filtered off and washed with cold benzene, followed by hot ethyl alcohol; they recrystallised from chlorobenzene, forming almost colourless crystals, m. p. 165° (decomp.; green melt), and gave a bluish-green colour with sulphuric acid. The product (as V) (Found : C, 84.1; H, 4.3. C₂₀H₁₈O₃ requires C, 84.1; H, 4.4%) is difficultly soluble in hot ethyl alcohol, but soluble in benzene; when heated as described above, it yielded its generators, separated as before.

Benzylidenephthalide. Phenanthraquinone (1 g.) and benzylidenephthalide (III) (*Org. Synth.*, Coll. Vol. 2, p. 61) (1.1 g.) in benzene (25 c.c.) were exposed to sunlight for 20 days (May); the quinone dissolved, and the resulting crystals were filtered off and washed with light petroleum (b. p. 50—60°). The product crystallised from xylene in colourless crystals, m. p. 310° (red-brown melt) (Found : C, 80.3; H, 4.1. C₂₂H₁₈O₄ requires C, 80.9; H, 4.2%). It gave no colour with sulphuric acid at room

* Toluene in sunlight acts as a reducing agent; e.g., phenanthraquinone is transformed into 9 : 10-dihydroxyphenanthrene (Benrath and Meyer, *J. pr. Chem.*, 1914, 89, 258).

temperature, but a violet colour at 100°; it was difficultly soluble in cold ethyl alcohol and benzene, but soluble in hot xylene. Its behaviour with alkalis is described on p. 997.

Thermal decomposition was carried out for $\frac{1}{2}$ hour at about 330° (bath temp.) as described above. The resulting mixture was separated as before.

1:1-*Di-p-xenylpropylene*.—Phenanthraquinone (1 g.) and the olefin (IVb) (Pfeiffer and Schneider, *J. pr. Chem.*, 1931, **129**, 129) were exposed to sunlight for 50 days (March—April). The benzene was evaporated off in a vacuum, and the residual dark oil extracted with hot ligroin (b. p. 100—150°). The extract, on slow evaporation in a vacuum, gave crystals, which recrystallised from ethyl alcohol in colourless crystals, m. p. 143° (orange melt) (Found: C, 88.9; H, 5.8. $C_{41}H_{30}O_2$ requires C, 88.8; H, 5.5%). 2:2-*Dixenyl-3-methylphenanthro-9':10'-1:4-dioxen* (as VI) when treated with sulphuric acid gave an olive-green colour after a few minutes at room temperature; it was soluble in benzene and hot ethyl alcohol.

The thermal decomposition was carried out as described above for $\frac{1}{2}$ hour at about 270° (bath temp.); the mixture was separated as before.

Diphenylketen. Phenanthraquinone (1 g.) and diphenylketen (Staudinger, *Ber.*, 1911, **44**, 1622) (2 g.) in 30 c.c. of benzene were exposed to sunlight for 3 months (March—May), the phenanthraquinone dissolving as before and the solution becoming brown. The crystals that separated were filtered off, washed with cold benzene, and recrystallised from hot benzene, forming almost colourless crystals, m. p. 227—230° (decomp.; orange melt) (Found: C, 83.5; H, 4.5. $C_{28}H_{18}O_3$ requires C, 83.6; H, 4.5%). The compound (VII) gave no immediate colour with sulphuric acid, but a dirty-green colour developed after some time; it was difficultly soluble in ligroin (b. p. 90—100°) and ethyl alcohol, but soluble in hot benzene; for its behaviour with alkali, see p. 997.

Thermal decomposition (15 mins. at bath temp. ca. 300°) afforded drops of an orange oil which solidified after 24 hours and were identified as phenanthraquinone.

as.-*Dixenylethylene*. Phenanthraquinone (1 g.) and the ethylene (IVc) (1.6 g.) (Pfeiffer and Schneider, *loc. cit.*) were exposed to sunlight for 3 months (March—June). The separated solid was collected, washed with cold ether and then with hot acetone, and recrystallised from benzene in colourless crystals, m. p. 234° (Found: C, 89.5; H, 5.3. $C_{40}H_{28}O_2$ requires C, 88.9; H, 5.2%). 2:2-*Dixenylphenanthro-9':10'-1:4-dioxen* (as VI), when treated with sulphuric acid, gave a red-brown colour at room temperature; it was soluble in hot benzene and difficultly soluble in ligroin (b. p. 90—100°).

For separation of the products of thermal decomposition (15 minutes at bath temp. ca. 290°), hot ligroin (b. p. 90—100°), in which (IVc) is soluble, was used.

1:1-*Di-p-anisylpropylene*. Phenanthraquinone (1 g.) and the olefin (IVa) (Pfeiffer and Wizinger, *Annalen*, 1928, **461**, 145) (1.1 g.) were exposed to sunlight for 3 months (March—June). The benzene was evaporated off in a vacuum and the brownish oily residue was extracted several times with ligroin (b. p. 70—80°). The extract, on slow evaporation, gave an almost colourless solid residue which recrystallised from benzene-light petroleum (b. p. 50—60°) in colourless crystals, m. p. 181° (orange-brown melt) (Found: C, 80.2; H, 5.6. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.6%). 2:2-*Di-p-anisyl-3-methylphenanthro-9':10'-1:4-dioxen* (as VI) when treated with sulphuric acid at room temperature gave a dark brown colour changing after a few minutes into olive-green; it was soluble in hot benzene, difficultly soluble in cold ethyl alcohol.

The products of thermal decomposition (bath temp. ca. 270°) were separated as in the preceding case.

(a, ii) *Photo-reaction between Retenequinone and Stilbene*.—Retenequinone (1 g.) and stilbene (0.7 g.) in 25 c.c. of benzene were exposed to sunlight for 21 days (March), the quinone then having dissolved. The benzene was evaporated off in a vacuum, and the solid residue was washed with cold light petroleum (b. p. 80—100°), and crystallised from ethyl alcohol, forming very light yellow crystals, m. p. 224—226° (decomp.; red melt) (Found: C, 86.8; H, 6.5. $C_{32}H_{26}O_2$ requires C, 86.5; H, 6.3%). 5:6-*Diphenyl-(1'-methyl-7'-isopropylphenanthro)-9':10'-1:4-dioxen* (VIII) gave no colour with sulphuric acid at room temperature, but a red colour at 100° and was soluble in hot benzene. At ca. 270° (bath temp.) it decomposed into retenequinone (identified, after recrystallisation from chloroform and ethyl alcohol, by mixed m. p. and colour reaction with sulphuric acid) and stilbene (recrystallised from ethyl alcohol and identified by m. p. and mixed m. p.). (This experiment was carried out with M. Z. Barakat.)

(b) *Action of Oxygen on Triarylmethanes in Sunlight*.—(1) *9- α -Naphthylxanthene*. Reduction of 9- α -naphthylxanthinhydratol (Gomberg and Schoepfle, *J. Amer. Chem. Soc.*, 1917, **39**, 1668) was carried out as described by Ullmann and Engi (*Ber.*, 1904, **37**, 2371) for the phenyl compound, i.e., by means of zinc dust and acetic acid with platinum chloride as a catalyst. 9- α -Naphthylxanthene recrystallised from benzene-light petroleum (b. p. 30—50°), m. p. 184° (Found: C, 89.5; H, 5.1. Calc. for $C_{23}H_{18}O$: C, 89.6; H, 5.2%). Kovache (*Ann. Chim.*, 1918, **10**, 184) gives m. p. 184°. It was soluble in benzene and gave no colour with sulphuric acid.

9- α -Naphthylxanthene was insolated for 5 days (February). The colourless crystals that separated were recrystallised from xylene; m. p. 228° (decomp.; dark melt) (Found: C, 85.3; H, 4.7. Calc. for $C_{40}H_{30}O_2$: C, 85.4; H, 4.7%). For the peroxide, Gomberg and Schoepfle (*loc. cit.*) gave m. p. 228—230°. The peroxide was practically insoluble in light petroleum (b. p. 30—50°) or in cold benzene, but soluble in hot benzene or xylene, and gave a deep red solution with sulphuric acid.

(2) *9- α -Naphthylthioxanthene*. To a Grignard solution of α -naphthylmagnesium bromide (magnesium, 1.2 g.; α -bromonaphthalene, 10.4 g.; dry ether, 50 c.c.), dry benzene (30 c.c.) was added, and the mixture treated gradually with powdered thioxanthone (Davis and Smiles, *J.*, 1910, **97**, 1296) (6 g.). The solution became yellow and a yellow precipitate formed; the mixture was refluxed for one hour, set aside overnight, poured into ice-cold dilute hydrochloric acid, extracted with ether, the extract dried, and the ether-benzene mixture evaporated. The residue, washed with cold ethyl alcohol and recrystallised from hot ethyl alcohol, had m. p. 191—192° (Found: C, 81.1; H, 4.3; S, 8.8. $C_{23}H_{18}OS$ requires C, 81.2; H, 4.7; S, 9.4%). 9- α -Naphthylthioxanthinhydratol was soluble in cold benzene, ether, and hot ethyl alcohol, and gave a red colour with sulphuric acid. It was reduced as in the preceding case, and the colourless 9- α -naphthylthioxanthene crystallised from benzene with one molecule of solvent of crystallisation, m. p. 77° (Found: C, 86.7; H, 5.5; S, 7.9. $C_{23}H_{18}S.C_6H_6$ requires C, 86.5;

H, 5.4; S, 7.9%). It was freely soluble in benzene, but difficultly soluble in ethyl alcohol; it gave no colour with sulphuric acid.

This xanthen was insolated for 4 days (February). The colourless crystals that separated, recrystallised from benzene-light petroleum (b. p. 30–50°), had m. p. 176° (efferv.). 9-*a*-Naphthylthioxanthyl peroxide (Found: C, 81.1; H, 4.4; S, 8.8. $C_{44}H_{30}O_2S_2$ requires C, 81.4; H, 4.5; S, 9.4%) is slightly soluble in hot benzene and soluble in hot xylene and gives a violet colour with sulphuric acid.

(3) 9-*m*-Tolylxanthen. 9-*m*-Tolylxanthhydrol, prepared substantially as for 9-*a*-naphthylthioxanthhydrol but from *m*-tolylmagnesium bromide (magnesium, 1.2 g.; *m*-bromotoluene, 9 g.; dry ether, 30 c.c.; dry benzene, 30 c.c.) and xanthone (5 g.), separated from benzene in colourless crystals, m. p. 149° (Found: C, 82.8; H, 5.6. $C_{30}H_{18}O_2$ requires C, 83.3; H, 5.5%). It was soluble in hot benzene and difficultly soluble in light petroleum (b. p. 30–50°) and gave a red colour with sulphuric acid.

Reduction of 9-*m*-tolylxanthhydrol was carried out as for the naphthyl analogue. The colourless 9-*m*-tolylxanthen, crystallised from ethyl alcohol, had m. p. 98° (Found: C, 88.1; H, 5.5. $C_{30}H_{18}O$ requires C, 88.2; H, 5.9%). It was difficultly soluble in cold ethyl alcohol, but soluble in hot ethyl alcohol or hot benzene; it gave no colour with sulphuric acid.

9-*m*-Tolylxanthen was insolated for 38 days (February–March), during which the benzene solution became yellow. The colourless crystals, obtained by evaporation of the benzene, followed by washing with absolute ethyl alcohol, were recrystallised from benzene-ethyl alcohol and had m. p. 205°. The peroxide (Found: C, 83.2; H, 5.4. $C_{40}H_{30}O_4$ requires C, 83.6; H, 5.2%) was soluble in cold benzene, but insoluble in hot ethyl alcohol; it gave a yellow colour with sulphuric acid.

(4) 9-*p*-Tolylxanthen. Reduction of 9-*p*-tolylxanthhydrol (Gomberg and Cone, *Annalen*, 1909, **370**, 164) was carried out as above. The colourless 9-*p*-tolylxanthen, crystallised from ethyl alcohol, had m. p. 116° (Found: C, 87.7; H, 5.9. Calc. for $C_{30}H_{18}O$: C, 88.2; H, 5.9%) (Kovache, *loc. cit.*, gives m. p. 116°). It gave no colour with sulphuric acid.

9-*p*-Tolylxanthen was insolated for 2 days (April). Colourless crystals, which began to separate after a few hours, were finally recrystallised from benzene; m. p. 217–218° (decomp.) (Found: C, 83.3; H, 5.6. Calc. for $C_{40}H_{30}O_4$: C, 83.6; H, 5.3%). Gomberg and Cone (*loc. cit.*, p. 166) give m. p. 212° (not sharp) for the peroxide. It dissolved with difficulty in light petroleum (b. p. 30–50°) and gave a brownish-red colour with sulphuric acid.

(5) 9-*p*-Methoxyphenylxanthen. Reduction of 9-*p*-methoxyphenylxanthhydrol (Gomberg and West, *J. Amer. Chem. Soc.*, 1912, **34**, 1528) was carried out as for the naphthyl analogue. The colourless xanthen, crystallised from ligroin (b. p. 70–80°), had m. p. 117° (Found: C, 82.9; H, 5.5. Calc. for $C_{30}H_{18}O_2$: C, 83.3; H, 5.5%) (Kovache, *loc. cit.*, gives m. p. 115°). It gave no colour with sulphuric acid.

9-*p*-Methoxyphenylxanthen was insolated for 30 days (February–March). The colourless crystals that separated were recrystallised from xylene, m. p. 205° (decomp.; dark brown melt) (Found: C, 79.1; H, 5.2. Calc. for $C_{40}H_{30}O_6$: C, 79.2; H, 4.9%). Gomberg and West (*loc. cit.*) give m. p. 214° (decomp.) for *p*-methoxyphenylxanthyl peroxide. It was soluble in boiling benzene and toluene, slightly soluble in cold benzene, and insoluble in light petroleum (b. p. 30–50°), and gave a red-brown colour with sulphuric acid.

(6) 9-Benzylxanthen. 9-Benzylxanthen (Decker, *loc. cit.*) (2 g.) was insolated for four months (April–August) in the presence of air. On slow evaporation of the benzene solution, it was recovered practically unchanged.

(c) Photochemical Reaction between Phenanthraquinone and Aromatic Aldehydes.—(i) 2:4-Dimethoxybenzaldehyde. Phenanthraquinone (1 g.) and the aldehyde (0.8 g.) in benzene (30 c.c.) were exposed to sunlight for 10 days (August). The colourless crystals that separated were washed with small amounts of cold benzene and crystallised from benzene, from which the 2:4-dimethoxyphenylhydroxymethylene ether of 9:10-dihydroxyphenanthrene (XIa) separated in colourless needles, m. p. 223° (red brown melt) (Found: C, 73.4; H, 4.8. $C_{23}H_{18}O_6$ requires C, 73.8; H, 4.8%). It was soluble in hot chloroform and benzene and difficultly soluble in hot ethyl alcohol; it gave a green colour with sulphuric acid.

(ii) Cuminaldehyde. Phenanthraquinone (1 g.) and cuminaldehyde (0.7 g.) in benzene (30 c.c.) were exposed to sunlight for 6 days (September). The resulting colourless crystals, recrystallised from ligroin (b. p. 80–90°), had m. p. 168–170° (decomp.; red melt). The benzene solution on concentration, gave a further amount of the cuminyldihydroxymethylene ether of 9:10-dihydroxyphenanthrene (XIc) (Found: C, 80.1; H, 5.3. $C_{24}H_{20}O_6$ requires C, 80.9; H, 5.6%). It was difficultly soluble in cold ethyl alcohol, but soluble in hot benzene; it gave an olive-green colour with sulphuric acid.

(iii) 2-Methoxy-1-naphthaldehyde. Phenanthraquinone (1 g.) and 2-methoxy-1-naphthaldehyde (0.9 g.) in benzene (30 c.c.) were exposed for 10 days (September). The benzene was evaporated in a vacuum, and the residue washed with hot ethyl alcohol and crystallised from ligroin (100–150°), forming colourless crystals, m. p. 190° (orange melt) (Found: C, 79.1; H, 4.6. $C_{26}H_{18}O_4$ requires C, 79.1; H, 4.6%). The 2-methoxy-1-naphthylhydroxymethylene ether of 9:10-dihydroxyphenanthrene (XIb) was soluble in benzene and difficultly soluble in hot ethyl alcohol; it gave a green colour with sulphuric acid.

(d) Action of Sunlight on Diphenyl Triketone.—Diphenyl triketone (2 g.) (*Org. Synth.*, Coll. Vol. 2, p. 244) in benzene (20 c.c.) was exposed to sunlight for 21 days (May). The benzene solution on evaporation in a vacuum, gave a yellow residue. The latter, on crystallisation from ligroin (b. p. 70–80°) gave yellow crystals, m. p. 95°, proved to be benzil (m. p. and mixed m. p.); yield ca. 70%. The dark experiment was negative.

187. *The Crystal Structure of the Orthorhombic Modification of 1 : 2 : 5 : 6-Dibenzanthracene. A Quantitative X-Ray Investigation.*

By J. MONTEATH ROBERTSON and J. G. WHITE.

The crystal and molecular structure of the orthorhombic modification of 1 : 2 : 5 : 6-dibenzanthracene has been determined by quantitative X-ray analysis. The molecular arrangement in the crystal is quite different from that found for other aromatic hydrocarbons (e.g., anthracene, coronene, or pyrene). There are four molecules in the unit cell and these each possess an exact centre of symmetry (space-group *Pcab*). The molecules lie approximately in layers along the 200 planes, to which they are tilted at an angle of about 31° ; 9 out of the 11 carbon atoms are separately resolved in the Fourier maps, and the bond lengths connecting these atoms can be directly measured. These vary from 1.38 to 1.45 Å.

An approximate calculation of the bond distances from the 12 stable valency-bond structures for dibenzanthracene is given, but there is less agreement with the observed values than was found in coronene and pyrene.

Unfortunately, the accuracy is not likely to be quite as high as in the other structures mentioned above. In the central ring of the molecule the resolution is good and here the error should not exceed ± 0.02 Å. In the outer parts of the molecule the bond-length variations (Fig. 3) must be considered rather doubtful. It is shown, however, that the co-ordinates given lead to better structure factor agreements than can be obtained from any regularised model.

RECENT X-ray measurements on coronene and pyrene (Robertson and White, *J.*, 1945, 607; this vol., p. 358) have established that the carbon-carbon bond lengths vary slightly in different parts of these molecules. These variations are small, in fact, not much greater than the possible experimental error under present conditions; nevertheless, the variations do seem to conform to a fairly definite pattern which is capable of at least partial explanation in terms of the more important structures which contribute to the normal states of these molecules.

We have now extended our measurements to 1 : 2 : 5 : 6-dibenzanthracene. This hydrocarbon exists in two distinct crystalline modifications, monoclinic and orthorhombic. Preliminary data for the monoclinic form have been given by Iball and Robertson (*Nature*, 1933, 132, 750). The orthorhombic form, with which we are concerned in the present paper, was first described by Krishnan and Banerjee (*Z. Krist.*, 1935, 91, 170, 173), who studied the magnetic anisotropy of the crystal and from their measurements of the magnetic susceptibilities were able to deduce the approximate orientation of the molecules. Accurate values for the cell dimensions, and a determination of the space-group have been given by Iball (*Nature*, 1936, 137, 361), but detailed atomic positions have not been given by any of these authors.

The crystal structure and molecular arrangement in orthorhombic dibenzanthracene differs from that of both the coronene and the pyrene structures. Like coronene, the molecules are found to display an exact centre of symmetry and to this extent the analysis is simplified. However, the unit cell contains four complete molecules and their mutual arrangement (see Figs. 1 and 2) makes it impossible to obtain resolution of all the atoms in any projection of the structures. In this respect the results obtained from the present two-dimensional analysis resemble the pyrene results, and they should similarly be regarded as a preliminary analysis, carried out with as much accuracy as possible, which must be undertaken before any further refinement by more elaborate three-dimensional methods can be attempted. In the present case the most favourable Fourier projection of the structure (Fig. 1) shows separate resolution of nine out of the eleven crystallographically independent carbon atoms, and direct measurements of these positions can be made. The results indicate certain bond-length variations, as shown in Fig. 3. These figures represent the most probable values, but they are unfortunately subject to certain errors. The accuracy in the central ring should be reasonably high, the errors here probably not exceeding ± 0.02 Å. In the other parts of the molecule the observed bond-length variations must be considered rather doubtful.

Description of the Structure.—*Crystal data.* 1 : 2 : 5 : 6-Dibenzanthracene, $C_{22}H_{14}$; M , 278.3; m. p. 267.5° ; d , calc. 1.294, found 1.282; orthorhombic bipyramidal, $a = 8.22$, $b = 11.39$, $c = 15.14$ Å. (Iball). Absent spectra, $(0kl)$ when l is odd, $(h0l)$ when h is odd, $(hk0)$ when h is odd. Space-group D_{2h}^{15} (or Q_h^{15}) (*Pcab*). Four molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell, 1418 Å^3 . Absorption coefficient for X-rays, $\lambda = 1.54 \text{ Å}$, $\mu = 6.78 \text{ cm}^{-1}$; $\lambda = 0.71 \text{ Å}$, $\mu = 0.86 \text{ cm}^{-1}$. Total number of electrons per unit cell = $F(000) = 584$.

Structure analysis. The space-group *Pcab* with only four molecules in the unit cell requires that the molecules must possess centres of symmetry which coincide with the crystallographic centres of symmetry. The asymmetric unit may therefore be taken as one half of the chemical

FIG. 1(a).

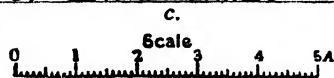
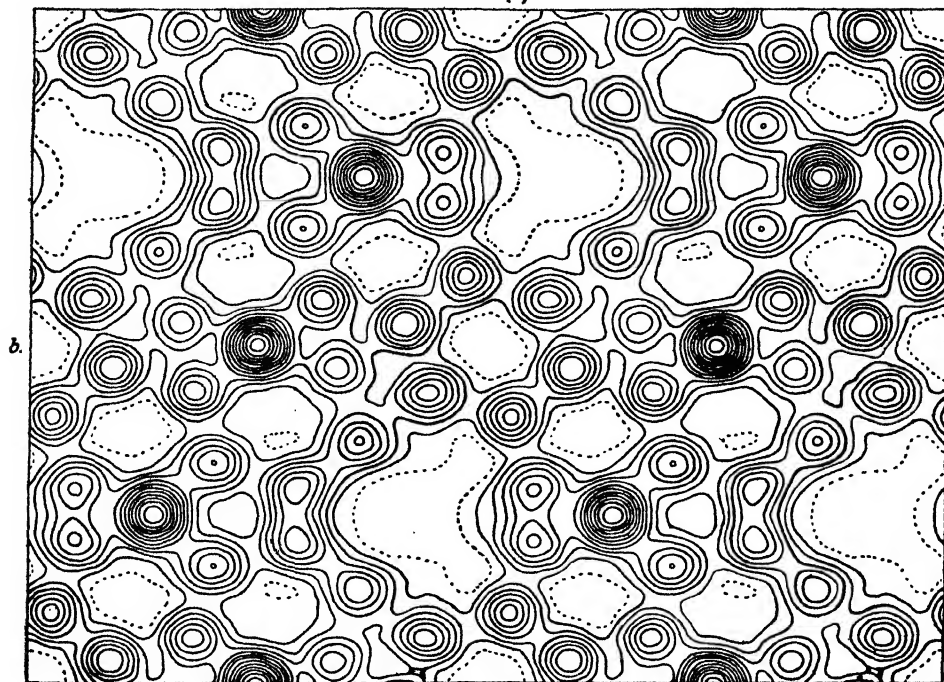
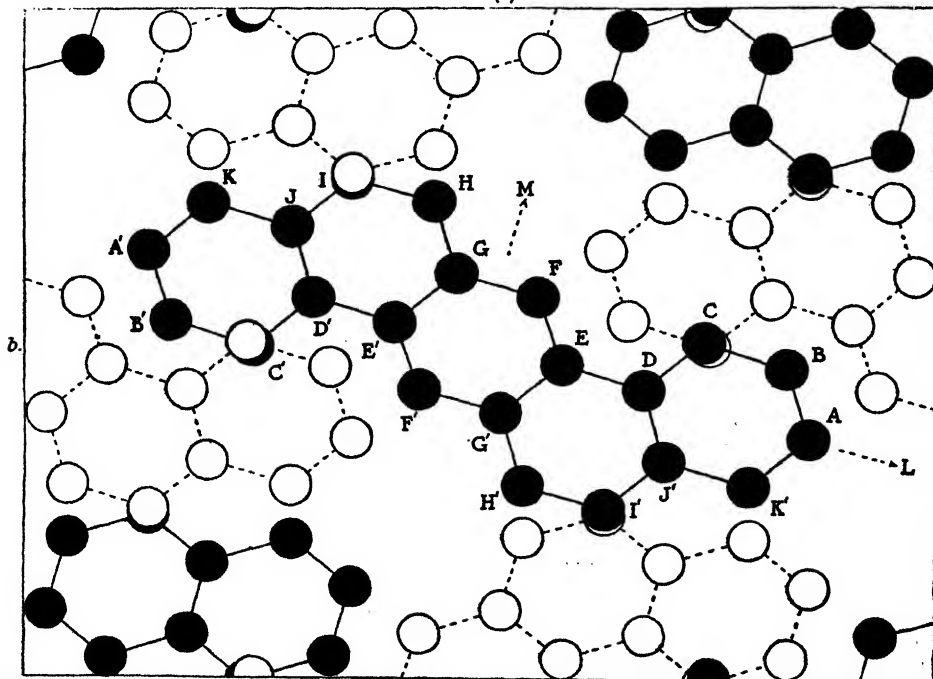


FIG. 1(b).



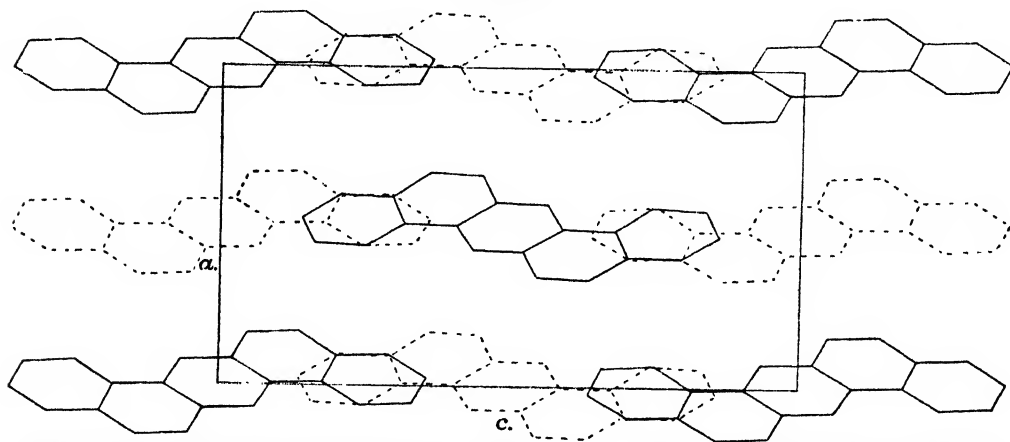
Projection along the *a* axis on the (100) or *bc* plane. The molecules are inclined at about 31° to the projection plane. Each contour line corresponds to a density increment of one electron per \AA^3 , the one-electron

molecule, or eleven carbon atoms, if we neglect the hydrogen atoms. As a first approximation a regular planar structure was assumed, according to the usual chemical formula.

The magnetic measurements of Krishnan and Banerjee (*loc. cit.*) give the tilt of the molecular plane to the *bc* plane as 29° , and these authors predict that the long axis of the molecule (*L* in Fig. 1*b*) probably lies along the *c* axis of the crystal. The first of these observations is probably fairly accurate, but the second can only be an approximation. Now, the strength of the (200) reflection ($F = 153$) suggests that if the molecular plane is inclined at about 30° to the *bc* plane, as the magnetic measurements suggest, then the line of zero tilt in the molecule must be its longest axis, that is, the molecular axis *L* must lie in, or very nearly in, the *bc* plane.

Bearing these factors in mind, only one degree of freedom remains to be fixed, the angle which *L* makes in the *bc* projections with the crystal axis *c* (or *b*). A suitably drawn projection of the molecules may then be pivoted about the centre of symmetry in the *bc* plane and the effect of various positions on the (*0kl*) structure factors may be tested by inspection or simple calculation. In practice the (020) structure factor was used as an index, as its low value ($F = 24$) makes it extremely sensitive. When the molecular axis *L* is made to coincide with the crystal axis *c* the calculated value of this structure factor is much too large, but it can be brought to the correct value by a rotation of about 16° away from the *c* direction. A further small rotation would make

FIG. 2.



View of the molecular arrangement projected on the 010 plane. The dotted molecules are situated half a translation along the *b* axis.

this structure factor pass through zero and assume a negative value, but this possibility can be ruled out by the calculation of certain other structure factors.

Detailed calculations on this basis gave reasonably good agreements between the measured and the calculated values of all the structure factors, and it was possible to proceed immediately to further refinement of the atomic positions by Fourier series methods. Two successive Fourier syntheses of the (*0kl*) zone were carried out, 50 terms being included in the first, and 56, all the reflections which could be observed in this zone, in the second. The results of this final synthesis are given by the contour map of Fig. 1(*a*), from which it can be seen that nine out of the eleven crystallographically independent atoms are resolved. The other two atoms, *C* and *I*, are obscured by the overlapping of related atoms in adjoining molecules as indicated in Fig. 1(*b*).

The *y* and *z* co-ordinates finally adopted were obtained from those actually measured on this map after a correction for incompleteness of the Fourier series due to Booth (*Nature*, 1945, 156, 51). In this method a Fourier synthesis of the same zone is carried out using the calculated instead of the observed values of the structure factors and omitting all terms which are omitted in the final Fourier synthesis. The resulting map was found to give certain small changes in the atomic positions and these shifts were added to the observed co-ordinates but with opposite sign. This led to a slight improvement in the agreements between the measured and the calculated values of the structure factors, as described below (Experimental Section).

The *x* co-ordinates of the atoms cannot be obtained directly, as the other possible projections would give little information because of overlapping effects. These co-ordinates can only be calculated on the assumption that the molecule is planar, but this assumption is well supported

by the agreements obtained between the calculated and the observed values of the structure factors for the other two zones.

A complete picture of the crystal symmetry may be obtained by considering Fig. 1 in conjunction with Fig. 2, which shows diagrammatically the projection along the b axis.

Orientation, co-ordinates, and dimensions. By assuming a planar molecule and averaging certain distances as described more fully in the Experimental Section, it is possible to calculate the orientation of the molecule. The results are given in Table I, where χ , ψ , and ω are the angles which the molecular axes L and M [Fig. 1 (b)] and their perpendicular, N , make with the a , b , and c crystallographic axes. These results give the inclination of the molecular plane to the (100) plane, expressed by χ_N , as 31.3° in reasonably good agreement with the value of 29° predicted by Krishnan and Banerjee (*loc. cit.*).

TABLE I.

Orientation of the molecule in the crystal.

$\chi_L = 92.1^\circ$	$\cos \chi_L = -0.0374$	$\chi_M = 58.8^\circ$	$\cos \chi_M = 0.5180$
$\psi_L = 106.1^\circ$	$\cos \psi_L = -0.2771$	$\psi_M = 35.3^\circ$	$\cos \psi_M = 0.8162$
$\omega_L = -16.2^\circ$	$\cos \omega_L = 0.9601$	$\omega_M = 75.2^\circ$	$\cos \omega_M = 0.2558$
	$\chi_N = 31.3^\circ$	$\cos \chi_N = 0.8545$	
	$\psi_N = 120.5^\circ$	$\cos \psi_N = -0.5069$	
	$\omega_N = 96.5^\circ$	$\cos \omega_N = -0.1130$	

The co-ordinates with respect to the crystal axes are collected in Table II; y_1 and z_1 are the co-ordinates of the resolved atoms measured directly from the Fourier projection, while y_2 and z_2 are the values finally adopted after correction for the incompleteness of the Fourier series. It will be seen that the difference is small. The co-ordinates of the two atoms C and I which cannot be directly measured are those which the atoms would have in a regular hexagonal molecule in the above orientation. These positions are in agreement with the appearance of the double peaks shown in Fig. 1(a) but the centres cannot be assigned with any great certainty.

Table II lists the co-ordinates (x, y, z) for the eleven carbon atoms in the asymmetric crystal unit; the co-ordinates of all the other atoms in the unit cell may be obtained from these by the relations appropriate to the space-group $Pcab$, viz.,

$$\pm (x, y, z; 1/2 + x, 1/2 - y, z; x, 1/2 + y, 1/2 - z; 1/2 - x, y, 1/2 + z)$$

TABLE II.

Co-ordinates. Centre of symmetry as origin; y_1 and z_1 are co-ordinates measured directly, y_2 and z_2 co-ordinates adopted after correction.

Atoms [cf. Fig. 1(b)].	$x, A.$	$y_1, A.$	$y_2, A.$	$z_1, A.$	$z_2, A.$	$2\pi x/a.$	$2\pi y_1/b.$	$2\pi z_1/c.$
A	-0.215	-1.580	-1.584	5.465	5.476	-9.4°	-50.1°	130.3°
B	0.444	-0.380	-0.392	5.094	5.108	19.4	-12.4	121.4
C	0.504	0.020	0.020	3.723	3.723	22.1	0.6	88.5
D	-0.095	-0.776	-0.770	2.738	2.740	-4.2	-24.3	65.1
E	-0.028	-0.370	-0.354	1.382	1.392	-1.2	-11.2	33.2
F	0.600	0.786	0.794	0.992	0.978	26.2	25.0	23.3
G	0.647	1.198	1.172	-0.384	-0.376	28.3	37.1	-8.9
H	1.328	2.400	2.404	-0.760	-0.740	58.2	76.0	-17.6
I	1.381	2.794	2.794	-2.097	-2.097	60.5	88.3	-49.8
J	0.769	1.980	1.978	-3.076	-3.063	33.7	62.6	-73.0
K	0.827	2.380	2.388	-4.452	-4.448	36.2	75.3	-105.9

The molecular dimensions and bond lengths may be calculated from these co-ordinates and are shown graphically in Fig. 3. The ringed atoms are those separately resolved in Fig. 1, and the bond distances between these atoms are the only ones which can be obtained directly.

From the orientation of the molecule and the co-ordinates given in Table II the molecular co-ordinates of the atoms may be calculated and these are collected in Table III.

Intermolecular distances. The closest distance of approach between atoms of different molecules occurs between the standard molecule and the reflected molecule at $(1/2 - x, y, 1/2 + z)$. Between C on the standard molecule and J on this reflected molecule the distance is 3.54 A., while between F and A' the atoms are 3.56 A. apart. Other distances in this direction are $CD' 3.76$ A., $CK 3.71$ A., $EB' 3.87$ A., and $FK 3.78$ A. The distances are not quite so close between the first molecule and the reflected molecule at $1/2 + x, 1/2 - y, z$, where the atom I on the standard molecule is 3.59 A. from D' on the reflected molecule, 3.75 A. from J , and 3.82 A.

TABLE III.

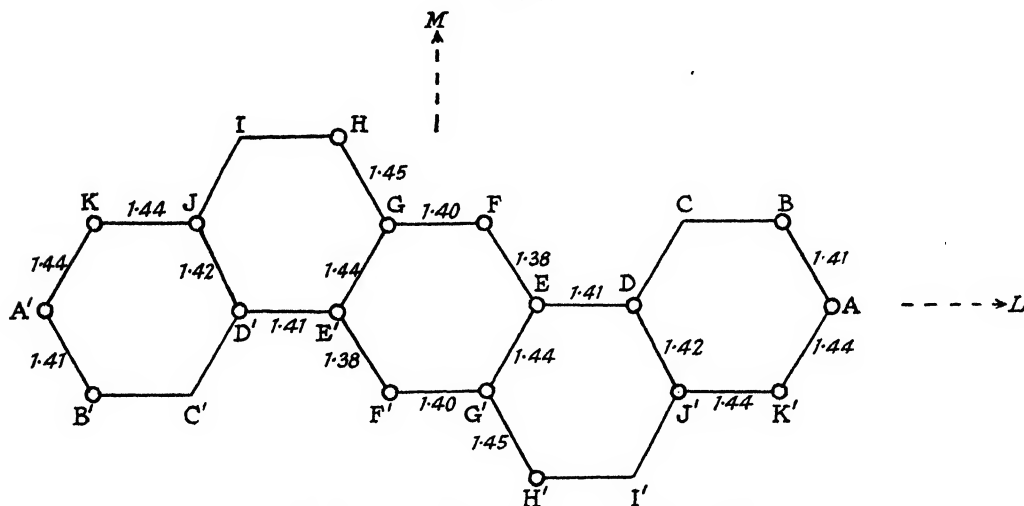
Co-ordinates with respect to molecular axes.

Atom.	L, Å.	M, Å.	N, Å.	Atom.	L, Å.	M, Å.	N, Å.
A	5.703	-0.003	0	G	-0.708	1.196	0
B	4.996	1.218	0	H	-1.427	2.460	0
C	3.550	1.230	0	I	-2.840	2.460	0
D	2.847	0.023	0	J	-3.520	1.229	0
E	1.435	0.050	0	K	-4.964	1.240	0
F	0.696	1.209	0				

from E'. All other pairs of atoms are more than 4 Å. apart, and the distances given above are just about the same as the usual intermolecular distances encountered in hydrocarbon structures.

It will be noted that in the dibenzanthracene structures all the primitive translations are greater than 8 Å., and we do not encounter pairs of molecules which directly overlie one another as in the phthalocyanine, coronene, or pyrene structures. It is therefore not profitable to discuss the normal projections of pairs of parallel molecules in this case, because they are widely separated and interleaved with parts of other differently oriented molecules.

FIG. 3.

*Dimensions of the molecule of 1 : 2 : 5 : 6-dibenzanthracene.*

Discussion of Results.—The bond-length measurements given in Fig. 3 vary from 1.38 to 1.45 Å., a slightly larger range than that found in coronene, and about the same as that found in pyrene (Robertson and White, *loc. cit.*). Unfortunately, the accuracy obtained in the present investigation is not likely to be quite as high as in these other structures. The unusually large values found for *GH*, *JK*, and *KA'* are very difficult to assess, as the atoms *H* and *K* are so distorted by their proximity to the corresponding atoms in the reflected molecule that their centres are rather more uncertain than those of the other resolved atoms. These bond lengths must therefore be considered as rather doubtful. The central ring, however, is quite free from any such distorting effects, and here the maximum error in the bond lengths should not be greater than ± 0.03 Å., and probably does not exceed ± 0.02 Å. The bond *GE* is, therefore, probably longer than the other two independent bonds in this ring, which are both very close to the benzene value of 1.39 Å.

Beyond this fairly definite conclusion little can be said with certainty. It will be noted that the dibenzanthracene molecule contains no symmetry element apart from the centre that can be used to average the bond lengths into any system of groups, as was done for coronene. However, the measurements recorded in Fig. 3 do receive a measure of general support from the very satisfactory agreements obtained between the observed and calculated values of the structure factors (Table IV). These agreements are better than can be obtained from any regular model placed in the same orientation.

For comparison with the results obtained for coronene and pyrene (Robertson and White,

is little agreement. The widest divergence is in the bond $K'A$, which is calculated as rather shorter than the benzene value and found experimentally longer than the graphite distance. As stated above, the position of K is rather uncertain, and under such conditions agreement could not be expected.

Structures (I) and (II) each contain four benzenoid rings, (III) and (IV) each contain three, and (V) and (VI) each contain only two, the remaining rings being quinonoid in type. If we attempt to apply the Fries rule, by preferring those structures which contain the largest number of benzenoid rings, the effect on the above calculations is disappointing. The bond lengths in the central ring tend to become equalised at the benzene value of 1.39 Å., and in the other parts of the molecule more extreme values are obtained, which are not in agreement with the observations.

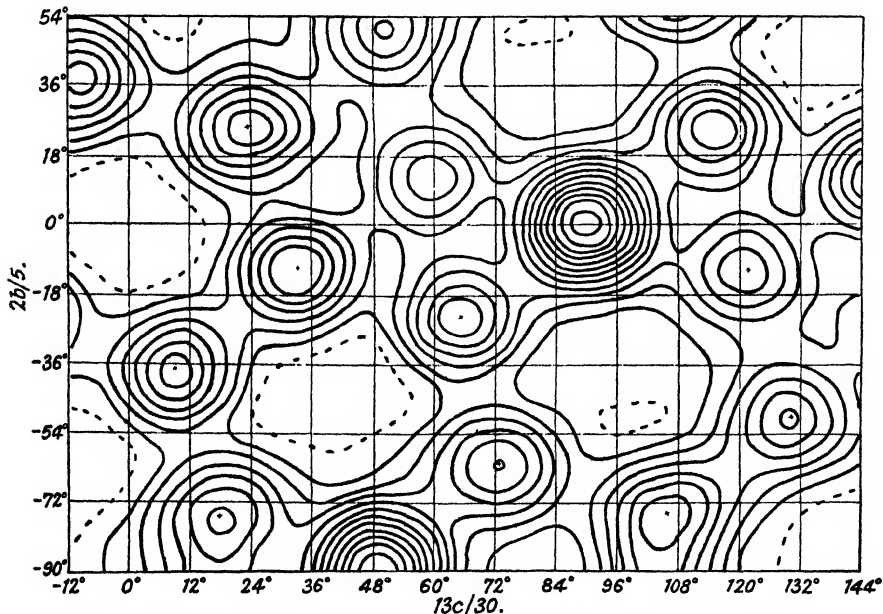
While lack of agreement in the outlying parts of the molecule may be due to experimental error to some extent, it should be noted that no rigorous theoretical derivation of bond lengths in a molecule of this shape has yet been made. It is possible that the excited structures (completely neglected in the above treatments) may play an appreciable part in such an asymmetric molecule, while in more symmetric molecules of the coronene type they may be relatively less important.

The calculated average value for the bond lengths in (VIII) is 1.41 Å., while the experimental average is 1.42 Å. The latter figure is, surprisingly, rather larger than that usually found in polycyclic aromatic hydrocarbons. It would, however, be necessary to determine the primitive translations of the crystal with greater accuracy before attaching undue importance to this average figure.

EXPERIMENTAL.

X-Ray Measurements.—Most of the X-ray work was carried out photographically with Cu- $K\alpha$ radiation ($\lambda = 1.54$), using rotation, oscillation, and moving-film methods. In addition, certain absolute measurements were made on the ionisation spectrometer, using monochromatic copper and molybdenum radiation.

FIG. 4.



Co-ordinates assigned to the resolved atoms in the bc projection of dibenzanthracene.

Some very beautifully formed specimens of the crystals were supplied by Dr. Iball, crystallised from ethyl acetate. These crystals appear to be remarkably stable and are little affected by exposure to X-rays; we have used some of them for many years as sub-standards for calibration purposes in absolute intensity work.

For the present investigation the intensity work was carried out mainly on three different specimens, which weighed 0.116, 0.081, and 0.0665 mg., respectively. These specimens were selected so that on rotation the path of the X-ray beam in the crystal did not vary by more than about 0.2 mm., and relative

TABLE IV.

Measured and calculated values of the structure factor.

<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	F, meas.	F, calc.	<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	F, meas.	F, calc.
002	0.102	50	-49	048	0.488	7	+4
004	0.203	13	-14	058	0.529	5	+8
006	0.303	10	+16	068	0.574	8	+12
008	0.407	30	-27	078	0.624	28	-27
00,10	0.508	16	-19	088	0.677	34	+31
00,12	0.610	< 5	- 6	098	0.731	13	-14
00,14	0.711	< 5	+ 3	0,10,8	0.789	< 5	0
00,16	0.812	< 4	+ 2	0,11,8	0.848	< 4	0
00,18	0.916	< 3	- 3	0,12,8	0.906	< 3	- 3
				0,13,8	0.968	< 2	- 2
020	0.135	24	+34	01,10	0.510	8	+7
040	0.270	55	+50	02,10	0.524	7	- 6
060	0.406	10	- 7	03,10	0.545	4	+ 2
080	0.541	15	- 6	04,10	0.573	6	-11
0,10,0	0.676	< 5	0	05,10	0.608	< 5	+ 8
0,12,0	0.810	< 4	- 1	06,10	0.648	< 5	+ 5
0,14,0	0.946	< 3	+ 2	07,10	0.693	6	- 6
				08,10	0.740	9	-11
200	0.188	153	+170	09,10	0.793	< 5	0
400	0.375	7	- 5	0,10,10	0.847	< 4	+ 1
600	0.562	< 5	- 3	0,11,10	0.901	< 4	0
800	0.749	5	- 8	0,12,10	0.957	< 3	- 2
				01,12	0.611	8	+ 7
012	0.122	28	+35	02,12	0.623	31	+42
022	0.169	4	- 2	03,12	0.641	27	+32
032	0.227	43	-36	04,12	0.665	9	+ 9
042	0.289	40	-38	05,12	0.696	< 5	+ 1
052	0.354	37	+30	06,12	0.731	4	+ 3
062	0.419	45	-43	07,12	0.712	< 5	+ 4
072	0.484	< 4	- 7	08,12	0.815	< 4	+ 2
082	0.551	< 4	- 1	09,12	0.861	< 4	- 1
092	0.617	< 5	- 2	0,10,12	0.910	< 3	- 2
0,10,2	0.684	< 5	+ 2	0,11,12	0.962	< 3	- 1
0,11,2	0.750	< 5	- 3	01,14	0.712	< 5	- 2
0,12,2	0.817	5	- 5	02,14	0.721	13	-14
0,13,2	0.883	6	+ 6	03,14	0.738	8	+ 8
0,14,2	0.952	< 3	- 3	04,14	0.760	< 5	- 3
014	0.214	26	+22	05,14	0.787	< 5	0
024	0.244	4	+ 5	06,14	0.818	< 4	- 1
034	0.287	34	-29	07,14	0.854	< 4	- 4
044	0.338	4	- 5				
054	0.394	6	+ 4	201	0.194	52	+54
064	0.454	7	+13	202	0.212	50	-41
074	0.515	4	+ 4	203	0.240	9	+11
084	0.578	< 4	- 5	204	0.275	10	-13
094	0.642	11	+11	205	0.314	7	- 5
0,10,4	0.707	24	+23	206	0.356	< 5	+ 5
0,11,4	0.772	26	+23	207	0.400	41	+36
0,12,4	0.835	< 4	+ 3	208	0.446	18	-12
0,13,4	0.901	< 4	- 2	209	0.492	< 7	+ 3
0,14,4	0.968	< 2	+ 2	20,10	0.539	< 7	+ 5
016	0.311	19	+23	20,11	0.587	30	+37
026	0.333	35	-27	20,12	0.635	14	+14
036	0.366	36	+33	20,13	0.684	13	-14
046	0.407	29	-28	20,14	0.732	< 8	+ 4
056	0.456	40	-40	20,15	0.786	7	+ 5
066	0.508	19	-19	401	0.378	17	-18
076	0.563	5	+ 6	402	0.388	< 6	+ 4
086	0.621	< 5	- 2	403	0.405	23	-20
096	0.681	6	- 4	404	0.426	36	-37
0,10,6	0.740	4	- 7	405	0.453	9	-12
0,11,6	0.795	< 5	-12	406	0.482	7	+ 2
0,12,6	0.867	< 4	- 1	407	0.516	14	+10
0,13,6	0.930	< 3	- 1	408	0.551	< 7	+ 8
0,14,6	0.994	< 2	- 2	409	0.590	15	-13
018	0.410	20	+21	40,10	0.630	< 8	+ 1
028	0.427	< 3	+ 2	40,11	0.671	28	+29
038	0.454	21	-25	40,12	0.714	15	+16

TABLE IV.—*continued.**Measured and calculated values of the structure factor.*

<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	<i>F</i> , meas.	<i>F</i> , calc.	<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	<i>F</i> , meas.	<i>F</i> , calc.
40,13	0.760	< 8	+ 1	260	0.448	13	+ 15
40,14	0.800	< 8	- 6	280	0.574	13	- 7
40,15	0.853	10	+ 6	2,10,0	0.703	< 9	- 3
601	0.565	12	- 14	320	0.312	76	- 76
602	0.570	10	+ 10	340	0.389	16	+ 15
603	0.582	9	+ 11	360	0.494	< 7	- 2
604	0.597	39	- 31	380	0.610	19	+ 15
605	0.616	8	- 9	3,10,0	0.733	16	+ 7
606	0.638	< 8	+ 3	420	0.399	60	+ 60
607	0.664	< 8	- 2	440	0.463	10	- 9
608	0.691	< 8	+ 4	460	0.553	9	+ 5
609	0.722	< 8	+ 3	480	0.659	< 8	+ 2
801	0.753	< 8	0	4,10,0	0.773	15	- 9
802	0.760	< 8	- 2	520	0.487	20	- 19
803	0.766	16	+ 12	540	0.541	< 8	- 12
804	0.780	10	- 5	560	0.620	16	+ 16
				580	0.716	< 9	0
120	0.165	71	- 71	5,10,0	0.823	11	+ 7
140	0.287	36	+ 34	620	0.578	9	- 10
160	0.417	17	- 20	640	0.624	14	+ 11
180	0.549	21	+ 19	660	0.693	7	- 7
1,10,0	0.682	< 8	0	680	0.780	< 8	+ 4
220	0.232	108	+ 108	720	0.870	< 8	0
204	0.330	10	- 8	740	0.710	< 9	- 2

absorption corrections for different reflections in the same zone were neglected. Most of the intensities were measured from calibrated films, using an integrating photometer of the type described by Robinson (*J. Sci. Instr.*, 1933, 10, 233). Only a few of the weakest reflections were estimated visually.

The absolute measurements were made directly on the ionisation spectrometer, with monochromatic rays, and also by means of sub-standards, employing the photographic technique (Robertson, *ibid.*, 1943, 20, 175). The usual formulae and correction factors for mosaic crystal specimens were employed.

Fourier Analysis.—Using the phase constants obtained initially from the trial structures and the measured values of *F*, a double Fourier series was set up according to the usual formulae. The electron density was computed at 450 points on the asymmetric unit, the *b* axis being divided into 60 parts (intervals of 0.190 Å.) and the *c* axis into 60 parts (intervals of 0.252 Å.). The summations were carried out by means of three-figure strips (Robertson, *Phil. Mag.*, 1936, 21, 176). The positions of the contour lines were obtained by graphical interpolation from the summation totals, by making sections of both the rows and columns. The resulting contour map is shown in Fig. 1, the whole unit cell being included.

Orientation of the molecule and co-ordinates. From an inspection of the observed lengths in projection of *ED* and parallel distances, which can be only very slightly tilted, it was found that the best average radius of the hexagons is 1.42 Å. With this average value and the assumptions that *L* and *M* are at right angles and that the molecule is planar, it was possible to calculate the orientation of the molecule with respect to the crystallographic axes.

The distances *FG'*, *EH'*, and *BK'* as measured from the projection given in Fig. 1 are 2.102 ± 0.040 Å., and from the assumed mean radius of the hexagons (1.42 Å.) the angle χ_M which *M* makes with the *a* crystal axis is obtained as 58.8° . The inclination of *L* cannot be derived in this way because it is very near to 90° . The calculation may, however, be made from the observed angle between *L* and *M* in the projection. The projected lines *ADE*, *BF*, and *K'J'G'* are inclined at a mean angle of $-16.1^\circ \pm 0.6^\circ$ to the *c* axis, and the lines *BK'*, *EH'*, and *FG'* make the mean angle of $72.6^\circ \pm 0.3^\circ$ with *c*. From these figures the complete orientation of the assumed regular planar molecule may be obtained by relations similar to those already given for the coronene analysis (Robertson and White, *loc. cit.*).

The next step consists of assigning the most probable positions to the centres of the resolved atoms, without the aid of any regularised model. The positions finally adopted after the Booth corrections for incompleteness of the Fourier series, etc., are shown by small crosses in Fig. 4. From these positions and the orientation now calculated, the actual molecular co-ordinates may be obtained (Table III), and the interatomic distances readily follow. The crystal co-ordinates are given in Table II.

The structure factors of the (*0kl*) zone have been recalculated on various assumptions, and the mean discrepancy, expressed as

$$\frac{\sum (|F_{\text{meas.}}| - |F_{\text{calc.}}|)}{\sum F_{\text{meas.}}}$$

has been evaluated with the following results. For a regular hexagonal model with a constant carbon-carbon distance of 1.42 Å. placed in the best orientation, the discrepancy is 16.1%. For the co-ordinates obtained directly from the contour maps (Figs. 1 and 4) without any assumptions about regularity (y_1 , z_1 in Table II), the discrepancy is reduced to 15.0%. After the Booth corrections, the final values for the co-ordinates, which are used for calculating the bond lengths (y_2 , z_2 in Table II), give a discrepancy of 13.8%. The differences between these figures are small, and their significance is difficult to estimate, but they do seem to justify the use of our final co-ordinates as being preferable to any set of regularised co-ordinates.

In calculating the structure factors the scattering curve formerly used for hydrocarbons (Robertson, *Proc. Roy. Soc.*, 1935, A, **150**, 110) was found to be rather unsuitable, as the calculated values for small spacing planes were consistently higher than the observed values. For the large spacing planes the tendency was for the observed structure factors to be larger than the calculated. In order to keep the upper part of the scattering curve at the usual values, all the absolute F 's were multiplied by a scale correction factor of 0.84 and then an empirical scattering curve was drawn for $\sin \theta = 0.5$ —0.9. The values used for this range are given below (max. $f_e = 100$).

$\sin \theta$ ($\lambda = 1.54$)	0.5	0.6	0.7	0.8	0.9
f_e	23.5	15.0	9.5	7.0	4.5

The general agreements calculated from the final co-ordinates are quite as good as are usually found in this type of analysis. The discrepancies are 13.8% for the (0kl) zone, 12.0% for the (hk0) zone, and 13.2% for the (h0l) zone. For all structure factors the mean discrepancy is 12.6%. The measured and calculated values of the structure factors are collected in Table IV.

We thank Professor J. W. Cook, F.R.S., and Dr. J. Iball for pure specimens of material used in this work, and Dr. Iball for much valuable preliminary data. We are also indebted to the Royal Society for a grant which defrayed the cost of some of the apparatus employed.

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[Received, November 4th, 1946.]

188. The Chemistry of Plutonium.

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A survey of some of the chemical and electrochemical properties of plutonium has been made. Valency states of 3, 4, and 6 have been established.

Oxidation and reduction reactions between the different valency states have been investigated. The reactions of plutonium ions with some of the commoner organic reagents are described.

PLUTONIUM was discovered late in 1940 by Seaborg, McMillan, Kennedy, and Wahl (*Physical Rev.*, 1946, **69**, 366; see also Seaborg, Wahl, and Kennedy, *ibid.*, p. 367). The investigations now reported were carried out with about 5 mg. of ^{239}Pu extracted from neutron-irradiated uranium. Experiments were carried out either with the plutonium in tracer concentrations, or else, by microchemical methods, with plutonium concentrations of the order of 1 mg. per ml.

^{239}Pu is an α -active nucleus with a half-life of 2.4×10^4 years (Seaborg, *Chem. Eng. News*, 1945, **23**, 2190).

I. *The Valencies of Plutonium.*—Plutonium was investigated in each of three well-defined valency states. It appears to be more stable to both mild oxidation and reduction when it is in the middle valency state of the three; in this condition, it was shown to be quadrivalent (see Experimental, A).

Polarographic experiments in plutonium solutions showed the presence of a wave at a half-wave potential of + 0.7 volt on the hydrogen scale. It was already known that plutonium could be oxidised to a valency state higher than 4, but the observed wave did not appear to be sufficiently positive to correspond to this process. It was therefore suspected that the wave corresponded to the reduction of plutonium to a state with a valency lower than 4. The existence of such a state was immediately confirmed chemically, and its valency was shown to be 3 by two methods (Experimental, B, i and ii), and that of plutonium in its highest oxidation state was shown to be 6 by the experiment described under B, iii.

II. *The Electrochemistry of Plutonium.*—Plutonium, like uranium, is a base metal and a transition element. Electrochemical studies were therefore mainly concerned with the processes of oxidation and reduction between the various valency states, and with complex formation. Evidence for complex formation is presented elsewhere (Sect. IV).

The potential of the Pu–Pu(III) couple. No indication of the potential of this couple has been obtained. The corresponding couple U–U(III) has a potential which has been estimated at – 1.5 volts (European sign convention) (Heal, unpublished work), and it is probable that the value for plutonium is not very different from this.

The potential of the couple Pu(III)–Pu(IV). The potential was determined both by direct measurement and polarographically (see C and D). The best characterised waves obtained are shown in Figs. 3a, 3b, and 3c. In all cases the diffusion current was lower for Pu(IV) than for Pu(III) solutions. The explanation of this phenomenon remains obscure.

The estimates of the molal oxidation–reduction potential given below were taken from the

direct determination in the case of sulphuric acid, and from the half-wave potentials in the other two cases :

In $1N-H_2SO_4$, + 0.72 volt at 23°. In $1N-HCl$, + 0.99 volt at 30°. In $1N-HClO_4$, + 0.86 volt at 23°.

These results show that the tervalent plutonium ion is a much less powerful reducing agent than the tervalent uranium ion (which liberates hydrogen from water). Indeed, the quadrivalent plutonium ion may be reduced to the tervalent state by the quadrivalent uranium ion. This reaction was studied polarographically at 30°, with the results recorded in E (Experimental).

III. *The Reactions of Plutonium.*—(a) *Oxidation-reduction reactions.* (i) In aqueous solutions, Pu(IV) may be reduced to Pu(III) by sulphur dioxide, hydroxylamine hydrochloride, the uranous ion, hydrazine hydrochloride, the iodide ion, electrolytically at a platinum cathode, or by shaking with mercury in chloride solutions.

The reaction with sulphur dioxide is slow at room temperature, but in hot solutions it goes to completion in about 5 minutes. The reduction of Pu(IV) by the iodide ion is also somewhat slow at room temperature in both sulphate and chloride solutions. The titration of the liberated iodine does not appear to be a useful method for the routine determination of plutonium.

(ii) Oxidation of Pu(III) by atmospheric oxygen is fairly rapid, and solutions of Pu(III) salts are completely oxidised to Pu(IV) on two or three evaporations to dryness in an open vessel in air. However, Pu(III) solutions are stable in an inert atmosphere. Permanganate oxidises Pu(III) quantitatively to Pu(IV) at room temperature in acid solutions. At 60°, the plutonium is oxidised to the hexavalent state.

(iii) In tracer concentrations of plutonium, the following oxidising agents were found to oxidise the Pu(IV) ion to the hexavalent state: hot potassium permanganate, potassium dichromate, argentic salts (including sodium perdisulphate in the presence of silver ions), and ceric ions. The conditions found to give satisfactory oxidation with perdisulphate and silver ions in these experiments are set out in section F (Experimental).

In concentrations of about 1 mg. per ml., Pu(IV) was oxidised to the hexavalent state by the following reagents: potassium permanganate in hot acid solution, hot sodium perdisulphate, argentic nitrate at room temperature, or hot bromate solutions containing nitric acid.

(iv) Pu(VI) is reduced to the ter- or quadri-valent state by sulphur dioxide, ferrocyanide ions, and hydrogen peroxide. The last reaction is complicated by a subsequent reaction between the hydrogen peroxide and the Pu(IV) ion to give a precipitate of a plutonium peroxide (see p. 1012).

(b) *Compounds of tervalent plutonium.* Solutions of tervalent plutonium salts are bright blue. The sulphate, chloride, and perchlorate are readily soluble in dilute acids. On addition of an excess of ammonium hydroxide a dirty blue precipitate of plutonium hydroxide is obtained. It may readily be redissolved in dilute acids to give solutions of Pu(III) salts.

The fluoride is insoluble in dilute acids, and tracer amounts of tervalent plutonium may be removed from solution by coprecipitation with lanthanum fluoride in the presence of hydrofluoric acid.

In the presence of hydroxylamine hydrochloride (to keep the plutonium in the reduced state), Pu(III) can be precipitated on a carrier of lanthanum oxalate. The removal of plutonium from the solution, however, was only 75% complete. The plutonium could be removed from the lanthanum oxalate carrier by washing with hot ammonium oxalate solution. It was not removed by ammonium oxalate solution at room temperature.

In acetate buffers at pH's of 3.6 and 5.6 it was found that Pu(IV) was much more completely removed from solution on a precipitate of bismuth oxychloride than was Pu(III); Pu(IV) ions therefore appear to be much more readily hydrolysed in solution than Pu(III) ions. To prevent losses of plutonium by adsorption on to glass, it is always necessary to work in acid solutions: $pH < 1$ is normally safe.

Pu(III) cannot be removed from acid solutions by coprecipitation with zirconium and one of the typical reagents for quadrivalent ions such as phenylarsonic acid or *m*-nitrobenzoic acid. Since Pu(IV) may readily be precipitated under these conditions, this enables a separation of Pu(III) from Pu(IV) to be carried out (see p. 1013).

(c) *Compounds of quadrivalent plutonium.* Solutions of the quadrivalent salts of plutonium are pale pink, with the exception of the nitrate, whose solutions are green.

Oxide, PuO_2 . Ignition of the nitrate, iodate, or hydroxide of quadrivalent plutonium at about 500–600° yields a dark brown oxide PuO_2 . In thin layers, the oxide appears to be yellow. If prepared by gentle ignition, it may easily be redissolved in hot concentrated

sulphuric or nitric acid. If ignited to a bright red heat, it dissolves readily only in potassium hydrogen sulphate at a dull red heat.

Hydroxide. The hydroxide is precipitated on the addition of ammonium hydroxide to solutions of Pu(IV) salts. It is a pale green gelatinous substance which can be centrifuged very readily. Precipitation of this hydroxide is one of the most convenient ways of removing plutonium from solution.

After being washed with dilute ammonium hydroxide and dried at 100°, the hydroxide dissolves readily in 1N-mineral acids, but decidedly more readily in nitric than in sulphuric or hydrochloric acid.

Peroxide. When hydrogen peroxide is added to an acid solution of a quadrivalent plutonium salt, a red-brown colour develops, and a bulky green precipitate of doubtful composition is slowly deposited. Precipitation of the plutonium is most complete in the pH range 3–4.5. The presence of sulphate ion appears to favour the reaction.

A precipitate of the same nature is obtained by adding hydrogen peroxide to solutions containing sexavalent plutonium, but it is formed less readily than from Pu(IV) solutions. It is therefore probable that the peroxide is a compound of quadrivalent plutonium, and that hydrogen peroxide reduces Pu(VI) to Pu(IV). The peroxide of plutonium is therefore quite different from uranium peroxide (peruranic acid). It is insoluble in sodium hydroxide solutions, and is presumably not a per-acid.

The peroxide dissolves in concentrated nitric acid with evolution of oxygen, to give a bright blue solution. When this solution is warmed, more oxygen is lost, and the blue solution fades to the pale green of Pu(IV) nitrate solutions. The peroxide may also be dissolved in 6% sulphurous acid solution.

The ratio of plutonium to peroxidic oxygen in the peroxide was determined by permanganate titration as described in the Experimental (G, i); if the permanganate reacted with the peroxidic oxygen in the same way as it does with hydrogen peroxide, the titration indicates that the ratio of atoms plutonium to atoms peroxidic oxygen is 2 to 3 (see G, ii). If the 0.335 mg. not accounted for is expressed as oxygen, the data give the following atomic ratios: Pu, 1; SO₄, 0.30; O (peroxidic and non-peroxidic), 2.93. The peroxide could therefore be written as PuO₃· $\frac{1}{3}$ SO₄. It is possible that the dried peroxide is different in composition from the original precipitate. Thorium, for example, forms two peroxides, Th₂O₇ (or Th₂O₇·SO₄) and ThO₃. The latter form is more stable than the former, and is obtained when the former is allowed to decompose (Pascal, "Traité de Chimie Minérale," Vol. 11, p. 289).

Fluoride. The fluoride of Pu(IV) coprecipitates very well with lanthanum fluoride. Experiments (see H) were carried out to determine the weight of lanthanum which must be precipitated as fluoride in order to obtain efficient carrying of the plutonium. Precipitation of plutonium on a lanthanum fluoride carrier under these conditions appears to be substantially complete when the weight of lanthanum precipitated is greater than about 0.1 mg. per ml. of plutonium solution.

The precipitation of plutonium fluoride in the absence of a carrier was uncertain: 0.35 mg. of Pu(IV) in 2 ml. of 1N-perchloric acid was not precipitated by the addition of 48% hydrofluoric acid. In higher concentrations of plutonium, a gelatinous precipitate was obtained which quickly collapsed to a dense yellowish powder, difficult to centrifuge off on account of its lack of coherence. The precipitation of an equal weight of lanthanum fluoride was found to bind the precipitate and eliminate this difficulty.

Sulphate, Pu(SO₄)₂. Evaporation of Pu(IV) solutions, prepared from the hydroxide and sulphuric acid or from the peroxide and sulphurous acid in the presence of sulphuric acid, followed by gentle ignition to remove the sulphuric acid, gives anhydrous *plutonium sulphate* as a light pink powder. The same compound is obtained when the oxide PuO₂ is fumed down to dryness with sulphuric acid. The anhydrous salt may be weighed in air. It is soluble in dilute mineral acids to give pale pink solutions. Dilute sulphuric acid solutions appear to be metastable, and sometimes a deposit of red-brown crystals is obtained on standing (Experimental, I).

Nitrate. Solutions of the nitrate in nitric acid are green. A sample of the hydrated solid nitrate was readily soluble in nitromethane.

Iodate, Pu(IO₃)₄. The iodate is obtained as a voluminous, very pale pink precipitate on addition of iodic acid or an iodate solution to solutions of Pu(IV) salts. It dissolves readily in 6% sulphurous acid solution, giving a solution containing tervalent plutonium.

Phenylarsonate. Pu(IV) is coprecipitated very efficiently from acid solutions on a precipitate of zirconium phenylarsonate, and the best pH range for this coprecipitation was investigated (Experimental, J), even strongly acid solutions being suitable.

In the presence of reducing agents (SO_2 or hydroxylamine hydrochloride), it was found that plutonium was not carried down at all by zirconium phenylarsonate. It was therefore concluded that the phenylarsonate of Pu(III) is soluble.

m-Nitrobenzoate. Pu(IV) may be precipitated on zirconium *m*-nitrobenzoate. The effect of pH on the completeness of the precipitation was investigated in the same way as with phenylarsonic acid (Experimental, K). In the presence of reducing agents, plutonium was not carried down on the precipitate of zirconium *m*-nitrobenzoate. It was therefore concluded that the *m*-nitrobenzoate of Pu(III) is soluble.

(d) *Compounds of sexavalent plutonium.* Ammonium plutonate. This salt may be prepared by adding ammonium hydroxide to a hot solution of a plutonium salt which has been oxidised to the sexavalent state with argentic nitrate; it is thereby obtained as a brownish-yellow precipitate which may be filtered off after it has cooled and stood until coagulated. The composition of ammonium plutonate has not been determined.

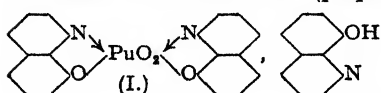
On account of the similarity between the chemistry of uranium and of plutonium in their sexavalent states, the terms "plutonate" and "plutonyl" have been used in the present paper to describe the sexavalent compounds of plutonium.

Plutonyl fluoride. Sexavalent plutonium is not precipitated on a lanthanum fluoride carrier in the presence of an excess of hydrofluoric acid. By this method, plutonium can readily be separated from lanthanum.

Plutonyl nitrate. Ammonium plutonate dissolves readily in nitric acid to give an orange solution, which, by analogy with uranium, is believed to contain plutonyl nitrate, $\text{PuO}_2(\text{NO}_3)_2$. At low pH values, the solution appears pink, and as the pH is increased, the colour becomes progressively more orange.

Ethyl ether and nitromethane extracted plutonyl nitrate from its aqueous solutions saturated with ammonium nitrate.

Sodium plutonyl acetate. Addition of sodium acetate solutions to a mixed plutonyl and ammonium nitrate solution (prepared by dissolving ammonium plutonate in nitric acid) slowly



precipitates crystals similar in appearance to those of sodium uranyl acetate, but pale mauve in colour. The compound is presumably sodium plutonyl acetate.

Plutonyl "oxinate." 8-Hydroxyquinoline ("oxine") precipitates plutonyl ions quantitatively in the pH range 3.5–9. The plutonium content of this oxinate was determined as described in Experimental (L). The weight of the complex obtained agreed with the structure (I) for the oxinate, which therefore appears to be the analogue of the corresponding uranyl complex.

IV. *Complex Formation by Plutonium.*—(a) *Inorganic complex ions.* The oxidation-reduction potentials for the Pu(III)–Pu(IV) couple are about +0.72 volt in 1N-sulphuric acid, +0.99 volt in 1N-hydrochloric acid, and +0.86 volt in 1N-perchloric acid. This variation indicates that there must be a tendency towards complex formation with the anion in at least two of the three acids, but the electrochemical evidence does not indicate in which acids this occurs. The presence of a high concentration of chloride ions inhibited the coprecipitation of Pu(III) on a lanthanum fluoride carrier, whereas the sulphate ion showed no real effect. This indicates that Pu(III) ions probably form complexes in chloride solutions. Similarly, ammonium thiocyanate completely inhibited the coprecipitation of Pu(IV) on a carrier of zirconium phenylarsonate or *m*-nitrobenzoate, thus indicating that Pu(IV) ions probably form complexes with the thiocyanate ion.

The presence of alkali carbonates interfered with the extraction of the acetylacetone complex of Pu(IV) into benzene. Experiments with visible quantities of plutonium showed that Pu(IV) salts, including the fluoride, dissolve completely in excess of ammonium carbonate.

Experiments with tracer amounts of plutonium showed that Pu(IV) coprecipitated with lanthanum oxalate could be washed off the lanthanum precipitate with hot or cold ammonium oxalate solution much more readily than could Pu(III). The solubility of Pu(IV) oxalate in ammonium oxalate was confirmed by using visible quantities of plutonium. Pu(IV) fluoride was also found to be readily soluble in ammonium oxalate solution.

(b) *Organic complexes of plutonium.* A brief survey of the behaviour of Pu(III), Pu(IV), and Pu(VI) towards some of the commoner organic complexing reagents was made. The results are contained in Experimental (M). In some cases, the reaction between the plutonium ion and the organic reagent was studied in more detail, using tracer concentrations of plutonium.

Diketone complexes. The extraction coefficient (defined as the ratio of the concentrations

of plutonium in the solvent and the aqueous layer) was measured at various pH's for the systems Pu(IV), water, benzene, and acetylacetone, trifluoroacetylacetone, or benzoylacetone. With the first two diketones, the extraction coefficient rose from 0.5 at pH 1 to an almost constant value of 80 at pH's of greater than 5 for acetylacetone and greater than 4 for trifluoroacetylacetone. The benzoylacetone gave a maximum extraction coefficient of 8 at a pH of 4. At higher pH's, the extraction coefficient decreased.

Salicylate complex. The extraction coefficient was measured for the system Pu(IV), amyl acetate, salicylic acid, and water at different concentrations of salicylic acid and at two different pH's. The detailed results are given in Experimental (N). In general, the extraction coefficient increased with increasing salicylate concentration in the aqueous layer, but at the higher pH, it was lower for a given salicylate concentration than for the same salicylate concentration at the lower pH. The irregularity of some of the results is believed to be due to the fact that a considerable proportion of the plutonium adhered to the glass walls of the vessels at the pH's used.

EXPERIMENTAL.

General Methods.—(a) *Preparation and purification of plutonium compounds.* During the present work, several methods were used for the initial purification of plutonium and for its recovery from the residues of previous experiments. The most useful method was found to be the one already described by Seaborg *et al.* (*loc. cit.*, p. 367) in which plutonium is precipitated with a carrier of lanthanum fluoride, and then separated from the lanthanum fluoride by making use of the solubility of the fluoride of hexavalent plutonium.

The plutonium in the ter- or quadri-valent state is precipitated on a carrier of lanthanum fluoride by the method described above. The precipitate is then dissolved by fuming with sulphuric or perchloric acid, and the solution is diluted with water. The plutonium is then oxidised to the hexavalent state: potassium permanganate in hot solution was found to be the most convenient oxidising agent for this purpose. The lanthanum is then precipitated by the addition of hydrofluoric acid, leaving the plutonium in solution.

The final purification of the plutonium may be carried out by evaporating the solution to fuming to eliminate the excess of hydrofluoric acid, reducing the plutonium to the tervalent state by warming with an excess of 6% sulphurous acid solution, and then precipitating the plutonium as Pu(OH)₃ by the addition of ammonium hydroxide.

The Pu(OH)₃ may then be dissolved in sulphuric acid, the plutonium converted to the quadrivalent state by evaporating the solution to dryness in air, and then successively precipitated as peroxide and iodate until the desired degree of purity has been reached.

(b) *Methods of determining plutonium.* Counting of α -particles provides a rapid method for carrying out determinations of relative amounts of plutonium when working with tracer quantities of the element. The half-life of ²³⁹Pu is 2.4×10^4 years (Seaborg, *loc. cit.*). This corresponds to the production of 138×10^6 α -particles/min./mg. Pu.

Plutonium may be weighed as Pu(SO₄)₂, PuO₂, or Pu(IO₃)₄. The sulphate is particularly convenient, since it may be prepared by fuming many plutonium compounds to dryness with sulphuric acid. The iodate is a useful form in which to weigh small amounts of Pu since it contains only 25.46% of Pu.

It has already been mentioned that permanganate titration of Pu(III) or Pu(IV) may be carried out in hot acid solutions. Titration of the iodine liberated in sulphate solution by the oxidation of iodide ions by Pu(IV) ions is not a convenient method for routine estimation of plutonium because the reaction is rather slow. In chloride solutions, the reaction is faster, but the titration is still not satisfactory.

(A) About 1 mg. of plutonium was purified and precipitated from sulphate solution as its insoluble iodate by addition of a solution of iodic acid. The precipitate was dried at 100° and weighed in a platinum crucible. It was then ignited to constant weight at a dull red heat in air. 3.532 Mg. of iodate gave a plutonium compound weighing 1.021 mg. after ignition. The loss of weight agrees well with the reaction $\text{Pu}(\text{IO}_3)_4 \rightarrow \text{PuO}_2 + 5\text{O}_2 + 2\text{I}_2$. The weights of iodate and oxide correspond to a valency of 3.92 for the middle oxidation state of plutonium. The 1.021 mg. of dioxide formed in this experiment was converted into sulphate by fuming to dryness three times with sulphuric acid. The sulphate weighed 1.616 mg.; *i.e.*, the sulphate contains 63.2% of PuO₂ [Pu(SO₄)₂ requires PuO₂, 62.9%].

(B) (i) During a determination of the oxidation-reduction potential of the Pu(IV)-Pu(IV-*n*) couple, it was found that a plot of the potential of a platinum electrode against the logarithm of the concentration ratio of Pu(IV) to Pu(IV-*n*) gave a straight line of slope 0.048 volt at 23°. This corresponds most nearly to the theoretical value of 0.059 volt for a single-electron transfer.

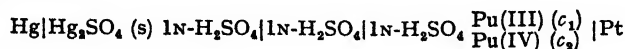
(ii) It was found that in sulphate solutions, the Pu(IV) ion will oxidise the iodide ion to iodine. The iodine which was liberated by 2.206 mg. of Pu(SO₄)₂ gave a titre of 0.47 ml. of 0.0103N-sodium thiosulphate. This corresponds to a valency difference of 0.95 between the middle and the lower state of plutonium.

(iii) 0.814 Mg. of Pu(SO₄)₂ was titrated in 1N-sulphuric acid solution with approximately 0.005N-potassium permanganate. Reaction was very slow at room temperature, but proceeded rapidly at 60°. After completion of the titration, the plutonium was reduced to the tervalent state by warming with sulphurous acid solution. The excess of sulphur dioxide was driven off by evaporating the solution to a very small volume in a stream of purified carbon dioxide. The tervalent plutonium was then titrated at room temperature to the quadrivalent state with the same permanganate solution. The end-point was quite definite and stable. On warming the solution to 60°, the pink colour of the end-

point faded, and a further quantity of permanganate reacted as the plutonium was oxidised to the highest valency state.

In four such cycles, the average volume of permanganate required to oxidise the Pu(III) to Pu(IV) was 0.37 ml. The volume required to oxidise the Pu(IV) to the highest valency state was almost exactly twice as much, *viz.*, 0.72 ml.

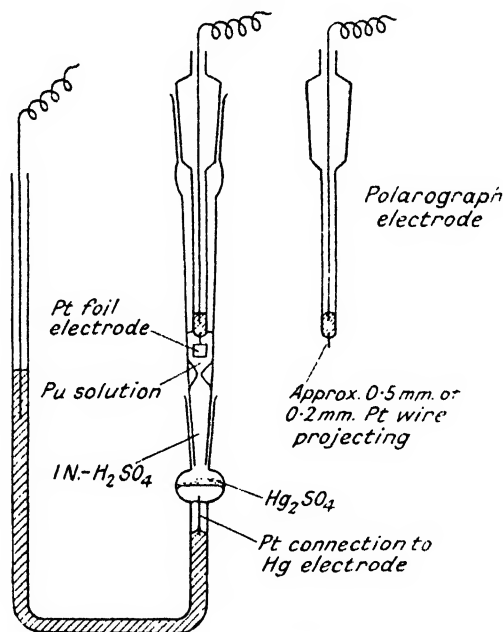
(C) Potentials of the cell



were measured. The cell is shown in Fig. 1.

The ratio of c_1 to c_2 was varied by mixing in various proportions stock solutions of Pu(IV) sulphate and of Pu(III) sulphate, both in 1N-H₂SO₄. The Pu(III) solution was made as and when required by both electrolytic reduction at a platinum cathode of a Pu(IV) solution.

FIG. 1.



Cell used for polarography and for E_0 measurements (half actual size).

The potentials were determined at 23°. They became steady within 5 mins. after insertion of the platinum electrode into the cell. The values are recorded below :

Potentials of the couple Pu(III)-Pu(IV).

Concn. of Pu(III) in solution, M.	Concn. of Pu(IV) in solution, M.	Potential, volt.	Concn. of Pu(III) in solution, M.	Concn. of Pu(IV) in solution, M.	Potential, volt.
0.00404	0.00058	0.0289	0.00152	0.00354	0.0825
0.00354	0.00118	0.0420	0.00101	0.00412	0.0931
0.00304	0.00177	0.0548	0.00051	0.00471	0.1050
0.00227	0.00265	0.0581			

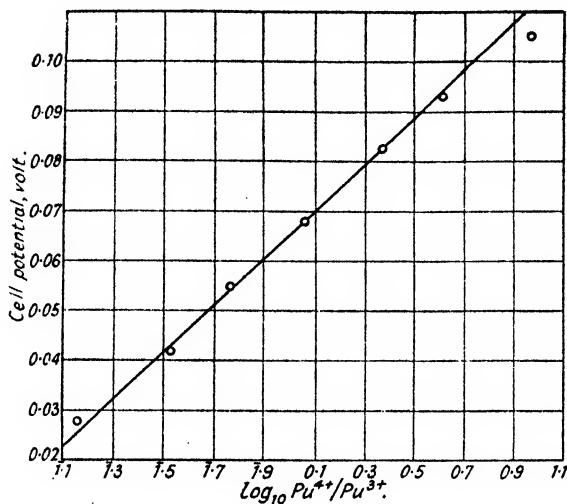
The molar concentrations were estimated by diluting a small volume of each of the stock solutions, and α -counting aliquots of the dilute solutions. There may thus be errors of up to 15% in the absolute concentration values, but as the same counter and counting technique were used for both of the solutions, the relative concentrations are believed to be correct to $\pm 5\%$.

Fig. 2 shows the linear variation of the potential with $\log_{10} c_2/c_1$. The potential when $c_2 = c_1$ was + 0.064 volt, with the platinum electrode positive. Assuming that the potential of the mercurous sulphate electrode is + 0.66 volt on the hydrogen scale, this gives a value of + 0.72 volt for the couple with equal concentrations. The molal standard potential is therefore in the region of + 0.72 volt.

Similar experiments designed to measure the potential of the same couple in 1N-hydrochloric acid and 1N-perchloric acid failed, because in several trials with different lots of plutonium the potentials drifted badly. However, the observed values of the equimolar potentials were always close to the potentials of the polarographic waves in the same solutions (see p. 1018).

(D) Polarographic experiments were carried out in 1*N*-sulphuric, -perchloric, and -hydrochloric acids (see Figs. 3, *a*, *b*, and *c*).

FIG. 2.



A small platinum wire micro-electrode replaced the foil electrode of the cell in Fig. 1, and a sintered-glass plug was substituted for the constriction. A dropping-mercury electrode could not be used because mercury dissolves anodically in the range of potentials studied. For polarograms in hydrochloric acid, a normal calomel reference electrode was used. For perchloric acid solutions, the reference electrode was Hg|Hg₂Cl₂(s) + 0.1*N*-HCl + 1*N*-HClO₄ with a bridge solution of 1*N*-HClO₄. In sulphuric acid, the reference electrode was Hg|Hg₂SO₄(s) + 1*N*-H₂SO₄.

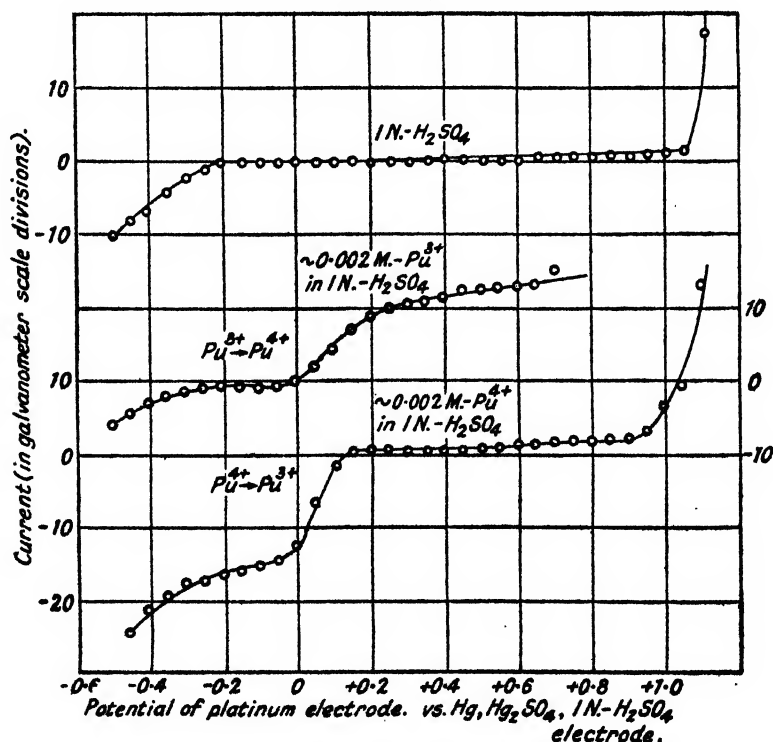
FIG. 3 (*a*).

FIG. 3 (b).

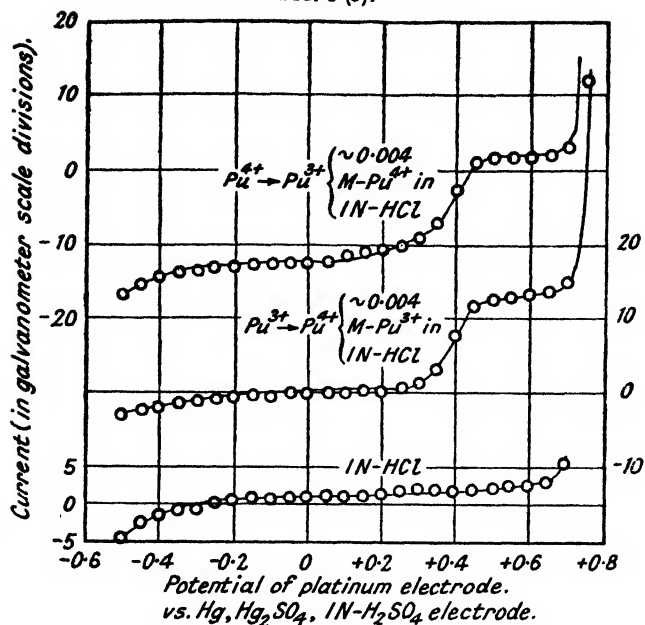
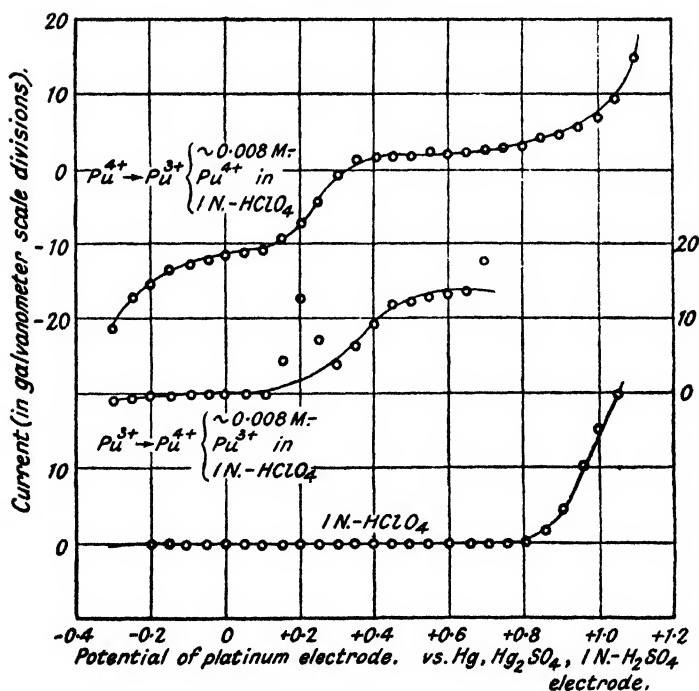


FIG. 3 (c).



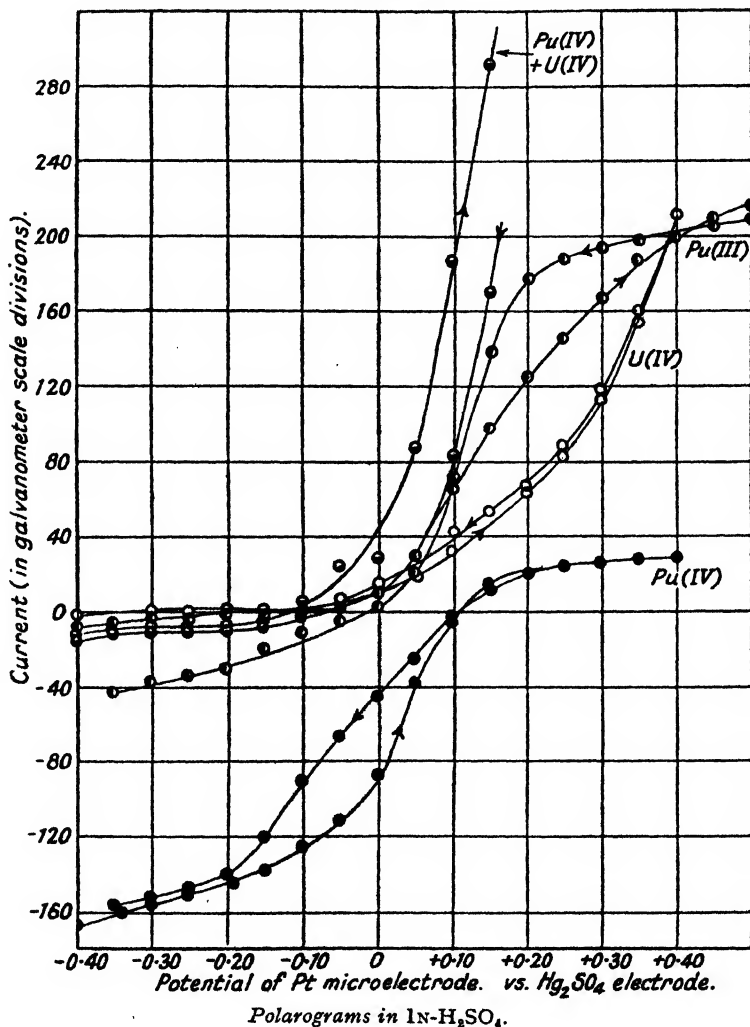
The polarograms in perchloric acid solution were carried out at 23°. In all other cases, the cell was held at 30° in a vibration-free thermostat.

(E) Small volumes of concentrated uranous sulphate and uranous chloride in their respective 1N-acids were added to solutions of Pu(IV) in 1N-sulphuric and hydrochloric acids. In both cases the Pu(IV) reduction wave disappeared within 2 or 3 minutes of the addition and was replaced by a wave starting

in the same place as the Pu(III) wave in the same solution (Figs. 4 and 5). The concentrations of Pu(IV) in these experiments were chosen so that after addition of the U(IV) solution, the Pu concentrations were equal to those used in plotting the polarograms for pure Pu(III) solutions given in the same diagram.

U(IV) in sulphuric and hydrochloric acids does not give an oxidation wave in this range of potentials. The great height of the oxidation wave in the Pu-U mixtures must be due to the oxidation of U(IV) at the electrodes in the presence of Pu(III), which acts as an electron carrier. (The uranium concentration was about 5 times the plutonium concentration.)

FIG. 4.



(F) Experiments were carried out in which the Pu(IV) ion was oxidised by the perdisulphate ion in the presence of silver ions. Different concentrations of reagents were tried, and the fraction of the plutonium which had been oxidised in the experiment was estimated by precipitating the remaining Pu(IV) on a carrier of lanthanum fluoride (the fluoride of sexavalent plutonium remains in solution under these conditions). The plutonium on the lanthanum fluoride carrier was then estimated by α -counting.

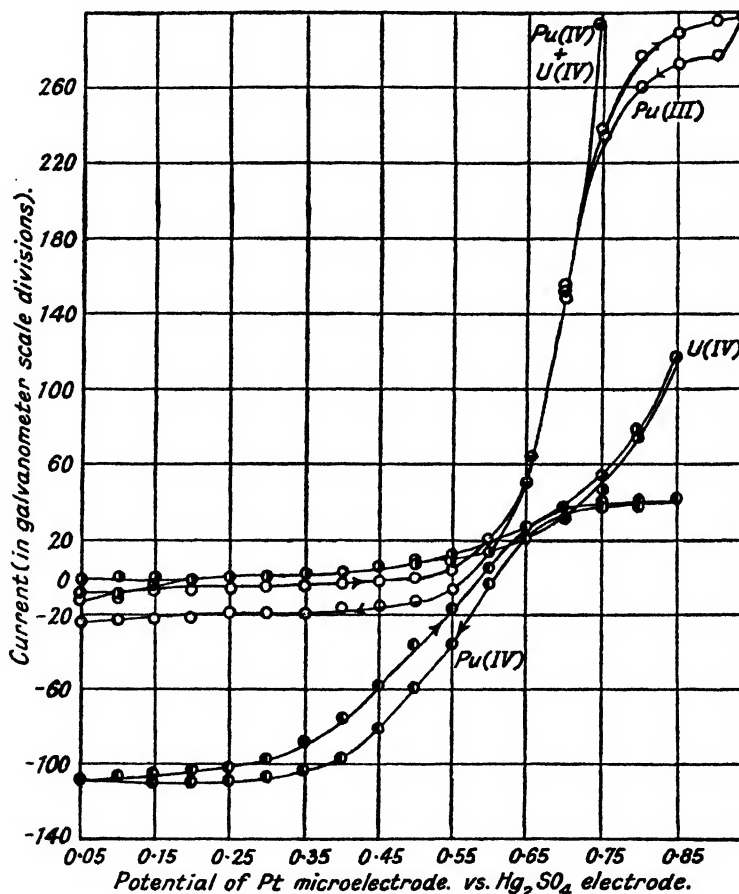
Concentrations of 0.2 mg. per ml. of silver ion and 2 mg. per ml. of perdisulphate ion were found to be sufficient. Oxidation of the plutonium took place when the solutions were heated to 80° and then allowed to cool and stand for 20 minutes. The presence of nitrate ions (about 0.5M) appeared to be advantageous. Perchloric acid up to 2M was without influence of the reaction.

(G) (i) A sample of plutonium peroxide precipitated from sulphate solution was washed free from excess of hydrogen peroxide, suspended in 1N-sulphuric acid, and titrated with potassium permanganate. It was found that on warming the solution very slightly, a reaction took place and the per-

oxide went into solution. After 0.71 ml. of permanganate had been used, the peroxide appeared to have dissolved completely, and further permanganate only reacted at a somewhat higher temperature. The volume of permanganate required at this higher temperature was 0.47 ml.

The second half of this titration was believed to represent the oxidation of Pu(IV) to Pu(VI). This was confirmed by reducing the plutonium to Pu(III) with sulphur dioxide, and evaporating the solution to fuming in air to remove the excess sulphur dioxide and convert the Pu(III) into Pu(IV). The same volume (0.47 ml.) of permanganate was used when the Pu(IV) obtained in this way was titrated to Pu(VI).

FIG. 5.



Polarograms in 1N-HCl.

(ii) A second sample of the peroxide, precipitated from sulphuric acid solution, washed three times with water, and dried to constant weight over silica gel at room temperature, was dissolved in concentrated nitric acid. The sulphate ion present in the solution was determined by precipitating it as barium sulphate. The plutonium was then precipitated from the solution as hydroxide and weighed as PuO_2 . The following results were obtained:

Wt. of peroxide, mg.	2.255
Wt. SO_4 , mg.	0.216
Wt. Pu, mg.	1.704
Total, mg.	1.920
Remainder, mg.	0.335

(H) A small weight of lanthanum nitrate in aqueous solution was added to a dilute perchloric acid solution containing a tracer quantity of quadrivalent plutonium; 48% hydrofluoric acid was then added until its concentration in the Pu-La solution was 12%. The precipitate of lanthanum fluoride was allowed to settle, and a further quantity of lanthanum nitrate, equal to the first amount, was then slowly added with good stirring.

After standing for about 80 minutes with occasional stirring, the solution was centrifuged to separate the fluoride precipitate. The supernatant solution was removed, and the precipitate washed several times with dilute hydrofluoric acid. The lanthanum fluoride was then spread on a sample tray, and the plutonium estimated by α -counting. The results are given below:

Precipitation of Pu(IV) on lanthanum fluoride.

Total wt. of La used, mg./ml. of Pu soln.	0.35	0.093	0.034	0.017
% Pu remaining in solution	1.49	1.94	6.11	10.4

(I) A sample of sulphate crystals (see p. 1012) was separated from the solution, washed with acetone, dried at room temperature and weighed. The sample was then converted into the anhydrous salt by fuming to dryness with sulphuric acid. The crystals were found to be the *tetrahydrate* [Found: $\text{Pu}(\text{SO}_4)_2$, 85.8. $\text{Pu}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$ requires $\text{Pu}(\text{SO}_4)_2$, 85.6%].

(J) Experiments were carried out to discover over what pH range zirconium phenylarsonate could be used as a carrier for tracer quantities of plutonium. Zirconyl nitrate solutions were added to dilute perchloric acid solutions containing tracer quantities of plutonium. The pH's of the solutions were then adjusted to various values by the addition of either more perchloric acid or ammonia. An excess of saturated aqueous phenylarsonic acid solution was then added, and the precipitate of zirconium phenylarsonate was removed by centrifuging, and its plutonium content estimated by α -counting. The results are shown herewith.

The precipitation of Pu(IV) on zirconium phenylarsonate.

pH	0.1	0.19	0.33	1.45	1.90	3.95
% Pu precipitated by 0.2 mg./ml. of Zr	87.6	88.5	93.9	93.7	90.0	93.2

(K) Precipitation of Pu(IV) on zirconium m-nitrobenzoate.

pH	0.39	1.46	1.88	3.80
% Pu precipitated by 0.2 mg./ml. of Zr	5.1 *	91.0	95.4	93.3

* Zr not completely precipitated.

(L) 9.457 Mg. of $\text{Pu}(\text{SO}_4)_2$ were dissolved in sulphuric acid and oxidised by heating for several hours at 90° on a steam-bath with an excess of sodium perdisulphate. The pH of the solution was then adjusted to about 5, and about 5 equivs. of oxine dissolved in acetic acid were added. The precipitate was coagulated by heating on the steam-bath, filtered off, washed with hot water, dried at 130°, and weighed. The *oxinate* weighed 15.713 mg. [Found: Pu, 33.4. $\text{PuO}_2(\text{C}_9\text{H}_6\text{ON})_2 \cdot \text{C}_9\text{H}_7\text{OH}$ requires Pu, 33.9%].

(M) Reaction of plutonium with organic complexing reagents.

Ion.	Reagent.	pH range.	Reaction.
Pu(IV)	Acetylacetone	2—10	Complex extractable in benzene
Pu(IV)	Benzoylacetone	3	Complex extractable in benzene
Pu(IV)	Monofluoroacetylacetone	3	Complex extractable in benzene
Pu(IV)	Trifluoroacetylacetone	2—4	Complex extractable in benzene
Pu(IV)	<i>p</i> -Dimethylaminobenzeneazophenylarsonic acid	4	Orange precipitate
Pu(III)	<i>p</i> -Dimethylaminobenzeneazophenylarsonic acid	4	No precipitate
Pu(IV)	<i>p</i> -Dimethylaminobenzeneazophenylarsinic acid	4	Orange-red precipitate
Pu(III)	<i>p</i> -Dimethylaminobenzeneazophenylarsinic acid	4	No precipitate
Pu(IV)	3-Nitro-4-hydroxyphenylarsonic acid	2.5	Pale greenish-buff precipitate, Pu carried down on Zr salt
Pu(III)	3-Nitro-4-hydroxyphenylarsonic acid	2.5	No ppt. Pu not carried down on Zr salt
Pu(IV)	<i>m</i> -Nitrophenylarsonic acid	2.5	Pale greenish-buff ppt. Pu carried down on Zr salt
Pu(III)	<i>m</i> -Nitrophenylarsonic acid	2.5	No ppt. Pu not carried down on Zr salt
Pu(IV)	Phenylarsonic acid	2	Pale greenish-buff ppt. Pu carried down on Zr salt
Pu(III)	Phenylarsonic acid	2	No ppt. Pu not carried down on Zr salt
Pu(IV)	<i>n</i> -Propylarsonic acid	2	Pale greenish-buff ppt. Pu carried down on Zr salt
Pu(III)	<i>n</i> -Propylarsonic acid	2	No ppt. Pu not carried down on Zr salt
Pu(IV)	<i>m</i> -Nitrobenzoic acid	1.5	Pale greenish-buff ppt. Pu carried down on Zr salt
Pu(III)	<i>m</i> -Nitrobenzoic acid	1.5	No ppt. Pu not carried down on Zr salt
Pu(IV)	Sebacic acid	1—2	Pu carried down on Zr salt
Pu(III)	Sebacic acid	1—2	Pu poorly carried down on Zr salt
Pu(IV)	5- <i>p</i> -Acetamidophenylazo-8-hydroxyquinoline	4	Complex extractable in amyl acetate. Insol. in water
Pu(IV)	8-Hydroxyquinoline	—8	Purple-brown ppt. extractable in amyl acetate

Ion.	Reagent.	pH range.	Reaction.
Pu(VI)	8-Hydroxyquinoline	4—8	Orange-brown ppt. extractable in amyl acetate
Pu(IV)	1'-Sulphonaphthalene-4'-azo-5 : 8-dihydroxyquinoline	3	Purple ppt.
Pu(IV)	Anthranilic acid	3	Complex extractable in amyl acetate
Pu(IV)	Cinnamic acid	2.5—4.5	Complex extractable in amyl alcohol
Pu(IV)	Cresotinic acid	2.5—4.5	Complex extractable in amyl acetate
Pu(IV)	2 : 4-Dihydroxybenzoic acid	3	Complex extractable in methyl isobutyl ketone
Pu(IV)	2 : 4-Dinitrosalicylic acid	3	Complex extractable in amyl acetate
Pu(IV)	Salicylic acid	2—3	Complex extractable in amyl acetate. Pu carried down on Th, La and Zr salts
Pu(IV)	Benzoic acid	2	Green-yellow ppt.
Pu(IV)	Citric acid	1—11	Soluble complex
Pu(IV)	Dihydroxytartaric acid	1	Pu carried down on Th salt
Pu(III)	Dihydroxytartaric acid	1	Pu poorly carried on Th salt
Pu(IV)	3 : 5-Dinitrobenzoic acid	3	Complex extractable in amyl acetate
Pu(IV)	Phthalic acid	2	Pu carried down on Zr salt
Pu(III)	Phthalic acid	2	Pu not carried down on Zr salt
Pu(IV)	Tartaric acid	1—11	Soluble complex
Pu(VI)	Tartaric acid	1—11	Soluble complex
Pu(IV)	Thiobarbituric acid	2	Pu carried down on Th, Zr, and La salts
Pu(III)	Thiobarbituric acid	3	Pu poorly carried down on Th, Zr, and La salts
Pu(IV)	" Cupferron "	0.5—2	Complex extractable in chloroform
Pu(IV)	Ethylenediamine	—	Brown ppt., insol. in water and organic liquids
Pu(IV)	α -Nitroso- β -naphthol	2	Complex extractable in methyl isobutyl ketone
Pu(IV)	Sodium benzenesulphinate	2	Buff ppt. not extractable in amyl acetate
Pu(VI)	Sodium benzenesulphinate	2	Complex extractable in amyl acetate
Pu(VI)	Sodium diethyldithiocarbamate	3	Purple-brown complex extractable in amyl acetate or amyl alcohol

(N) Extraction of Pu(IV) salicylate into amyl acetate.

Salicylate concn. in aq. layer, moles/l.	pH of aq. layer.	Extrn. coeff. of Pu.	Salicylate concn. in aq. layer, moles/l.	pH of aq. layer.	Extrn. coeff. of Pu.
0.0058	4.0	0.23	0.053	5.2	0.15
0.0116	4.0	0.16	0.214	5.2	0.22
0.0232	4.0	0.64	0.428	5.2	3.7
0.0464	4.0	7.9	0.642	5.2	4.8
0.0696	4.0	3.4	0.856	5.2	2.1
0.0928	4.0	4.7	1.07	5.2	12.8
0.116	4.0	8.12			

This work was carried out for the National Research Council of Canada, Atomic Energy Division, at Montreal, Que., and Chalk River, Ont. Two of the authors (B. G. H. and A. G. M.) were on leave from Messrs. Imperial Chemical Industries, Ltd. The authors are indebted to Mr. A. J. Cruikshank for help with some sections of the work

CHALK RIVER, ONTARIO.

[Received, March 6th, 1947.]

189. Production of Antibiotics by Fungi. Part III. Javanicin. An Antibacterial Pigment from *Fusarium javanicum*.

By H. R. V. ARNSTEIN and A. H. COOK.

The isolation and characterisation of *javanicin* is described. It is regarded as a 5 : 8-dihydroxy-6-acetonyl-1 : 4-naphthaquinone carrying additional β -methyl and β -methoxyl groupings.

It was observed (Arnstein, Cook, and Lacey, *Nature*, 1946, **157**, 333; see also Part I, Cook and Lacey, *Brit. J. Exp. Path.*, 1945, **26**, 404) that certain metabolism solutions obtained from *Fusarium javanicum* inhibited the growth of *Staphylococcus aureus* at a dilution of 1 : 100 and were also very active against the acid-fast *Mycobacterium phlei*. In view of the possibility of the active principle or principles having a useful inhibitory action against *M. tuberculosis* their nature

was studied more closely. Their production under various conditions and some biological properties are described elsewhere (Part II, Arnstein, Cook, and Lacey, *Brit. J. Exp. Path.*, 1946, 27, 349) and the present communication records experiments on their chemical nature.

The materials of the present study were only produced under selected conditions; the most notable requirement was the presence of "Bactotryptone" in addition to mineral salts and glucose in the fermenting solution. Bactotryptone could be replaced by some but not all similar preparations, though the characteristic essential for the production of antibacterial activity could not be distinguished. Under the selected conditions the active solutions were heavily pigmented, resembling red ink in colour. The activity could be completely removed from slightly acid solutions by extraction with solvents such as ether, and the crude recovered pigment accounted for the whole of the activity of the original solutions. After preliminary experiments had shown that the antibacterial activity was insensitive to heat, acid, alkali, and solvents, attempts were made to purify the active principles, for example, by the ordinary methods of chromatography but without success. It was found that the active principle could be removed from the crude ethereal extract by shaking with sodium carbonate but not by sodium hydrogen carbonate, and that it could be returned from aqueous sodium carbonate to ether by neutralising the solution. The final solution was still strongly coloured (red-orange) and, as inactive pigment fractions were rejected at each point, it was apparent that several probably chemically similar pigments were initially present. The active solution on concentration gave a pigment which could be crystallised. The behaviour of the crystalline material varied from batch to batch. One compound, m. p. 207.5–208° (decomp.), was invariably obtained and sometimes another compound, m. p. 213–214° (decomp.), formed a second component. Occasionally a product, m. p. 178–179°, was obtained which was analytically intermediate between the two compounds, and as the m. p. behaviour was reproduced by an equimolecular mixture of the two it seems not unlikely that the third product was a molecular compound of the other two. Both compounds were very active antibacterial agents (see Arnstein, Cook, and Lacey, *loc. cit.*) and there was no reason to doubt that the whole of the activity of the original solutions was due to these two crystalline pigments. They were very similar in character but detailed attention could be given only to the compound, m. p. 207.5–208°, which, as it does not appear to have been isolated previously, is conveniently termed *javanicin*; the compound, m. p. 213–214°, contained one oxygen atom more than *javanicin* and is therefore termed *oxyjavanicin*.

The pigments produced by *Fusaria* are known to be very variable and delicately dependent on the conditions of growth (Brown and Horne, *Ann. Bot.*, 1924, 38, 379; Brown, *ibid.*, 1925, 39, 373; Sideris, *J. Agric. Res.*, 1925, 30, 1011); probably for this reason there have been few occasions when *Fusarium* pigments have been isolated in pure condition and studied chemically. Ashley, Hobbs, and Raistrick (*Biochem. J.*, 1937, 31, 388) isolated two pigments, rubrofusarin and aurofusarin, from *F. culmorum*. Aurofusarin is so different from the present pigments that it can hardly be confused with them, whilst the distinctive nature of rubrofusarin is made clear below. *Javanicin* and *oxyjavanicin* differ from the earlier pigments in diffusing into and being isolated from the medium instead of from the mycelium; the mycelium of *F. javanicum* although coloured did not yield any remarkable quantity of antibacterial pigment. Solid media on which *F. javanicum* was grown also became deeply pigmented; on the other hand, those on which *F. culmorum* was grown were scarcely coloured although the mycelia were very bright (Brown and Horne, *loc. cit.*). Mull and Nord (*Arch. Biochem.*, 1944, 4, 422) mention diffusing *Fusaria* pigments and the experiments of Sideris (*loc. cit.*) particularly clearly demonstrate their formation, so the production of *javanicin* and *oxyjavanicin* is possibly not restricted to *F. javanicum*, and other species may produce nearly related pigments.

Javanicin contained only carbon, hydrogen, and oxygen. It apparently contained no easily hydrolysed groupings and could be heated in an autoclave without significant loss of activity, though very dilute solutions on prolonged exposure to light lost both colour and antibacterial activity, presumably as a result of photochemical oxidation.

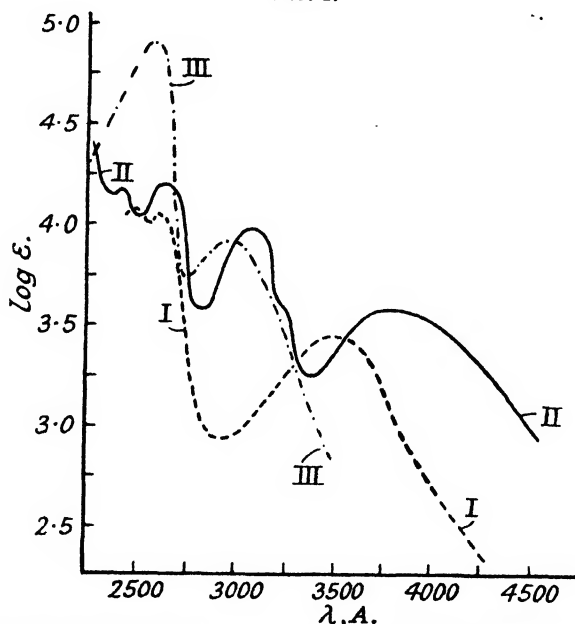
Analyses and determinations of molecular weight on different samples of *javanicin* from several batches indicated the formula $C_{15}H_{14}O_6$. Of the six oxygen atoms one was present as a methoxyl group. The molecule contained three active hydrogen atoms, but on acetylation in presence of concentrated sulphuric acid it yielded a yellow compound of the empirical and molecular formula, $C_{17}H_{14}O_6$, i.e., a monoacetyl derivative of a hitherto unknown anhydro*javanicin*. This *monoacetylanhydrojavanicin* contained one methoxyl group.

The reality of the dehydration of *javanicin* during acetylation was confirmed by the behaviour of the pigment itself. *Javanicin* showed signs of undergoing dehydration in sulphuric acid solution and under other conditions, but reaction was most satisfactory with ethereal hydrogen

chloride containing zinc chloride. Under these conditions javanicin smoothly lost 1 mol. of water to give *anhydrojavanicin*, $C_{18}H_{12}O_8$, which on acetylation passed into the acetyl compound previously obtained directly. Anhydrojavanicin was chemically and physically quite distinct from the parent pigment, and contained only one active hydrogen atom in agreement with structure (III) ($R = H$) developed below. Two more oxygen atoms were revealed as a quinone grouping, for on reductive acetylation anhydrojavanicin was converted into a *leucoanhydrotriacetate*, $C_{21}H_{20}O_8$.

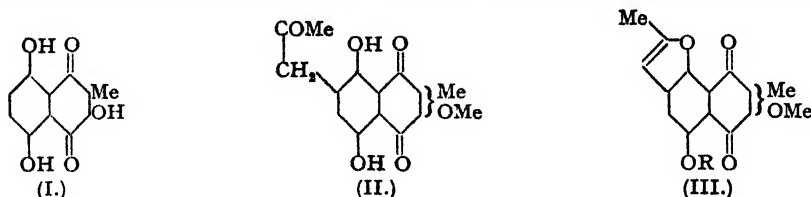
Javanicin anhydromonoacetate and leucoanhydrotriacetate showed spectra which indicated them to be α -naphthaquinone and naphthalene derivatives respectively (Fig. 1). It is known that if the hydroxyl groups of a hydroxynaphthaquinone be acylated, the spectrum loses any features peculiar to the tautomeric hydroxynaphthaquinone structure and reverts to that of a simple naphthaquinone (Macbeth, Price, and Winzor, *J.*, 1935, 325). Incidentally, consideration of the spectra of javanicin and its derivatives excluded the possibility of their being benzoquinone or anthraquinone derivatives; it was moreover impossible to accommodate a summation of other facts noted below on these formulations. Rubrofusarin, $C_{18}H_{12}O_8$, a pigment from

FIG. 1.

I. *Hydroxydroserone triacetate*.II. *Javanicin anhydromonoacetate*.III. *Javanicin leucoanhydrotriacetate*.

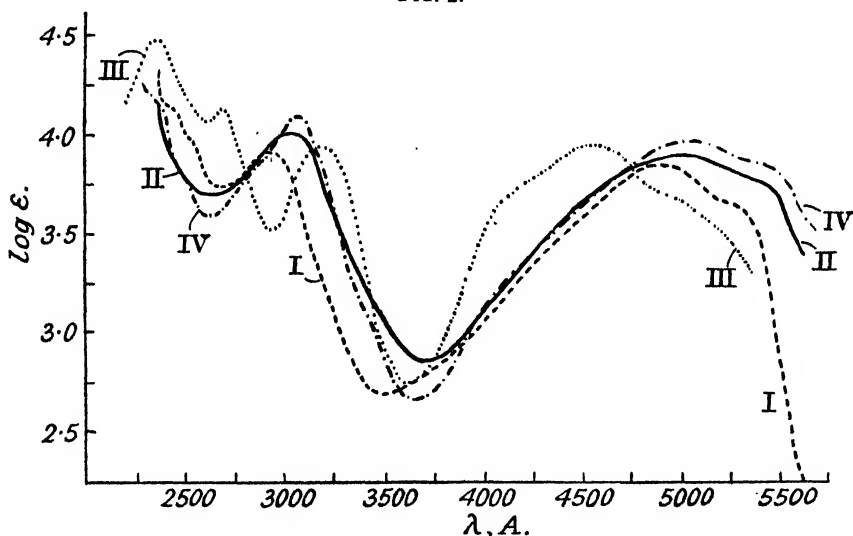
F. culmorum (Ashley, Hobbs, and Raistrick, *loc. cit.*) appears formally closely related to javanicin, but rubrofusarin behaves quite differently especially towards alkalis, with which it gives only a yellow colour, gives derivatives which are clearly distinct from those of javanicin, and is also spectrally quite distinct from javanicin (cf. Mull and Nord, *loc. cit.*). Javanicin gave a deep violet solution with 10% sodium hydroxide, purple solutions with concentrated ammonia or 2*N*-sodium carbonate, but no colour with sodium hydrogen carbonate. It was decolorised by bromine water or aqueous sodium hydrogen sulphite. The formulation of javanicin as a naphthaquinone derivative was supported by its colour reaction with lead acetate in methanol. Javanicin gave a violet solution; methyl-naphthazarin also gave a violet solution, whilst hydroxydroserone (see below) gave a violet precipitate, and Kuhn and Wallenfels (*Ber.*, 1939, 72, 1411) record that 5 : 8-dihydroxy- and 2 : 5 : 8-trihydroxy-naphthaquinone, echinochrome A, and its trimethyl ether all give violet solutions or precipitates. The formation of a coloured solution rather than a precipitate indicated the absence of any β -hydroxyl group (cf. Kuhn and Wallenfels, *loc. cit.*; see also below). Reaction of javanicin with diazomethane was complex, presumably because of reaction with the side chain, but anhydrojavanicin failed to react under normal conditions. As anhydrojavanicin is regarded as having the angular structure (III), and as only β -hydroxyl

groups in naphthaquinones are methylated under the normal conditions by diazomethane (Kuhn and Wallenfels, *loc. cit.*), this behaviour provides further though indirect evidence of the methoxyl group occupying a β -position. Comparison of the absorption spectrum of javanicin with that of representative hydroxynaphthaquinones revealed that its spectrum was practically



coincident with that of hydroxydroserone (Macbeth, Price, and Winzor, *loc. cit.*) (Fig. 2) (3:5:8-trihydroxy-2-methyl-1:4-naphthaquinone, I) and the sequel shows that javanicin is indeed closely related structurally to hydroxydroserone, which also gives a magnificent violet colour with alkali (Rennie, *J.*, 1887, 51, 374).

FIG. 2.



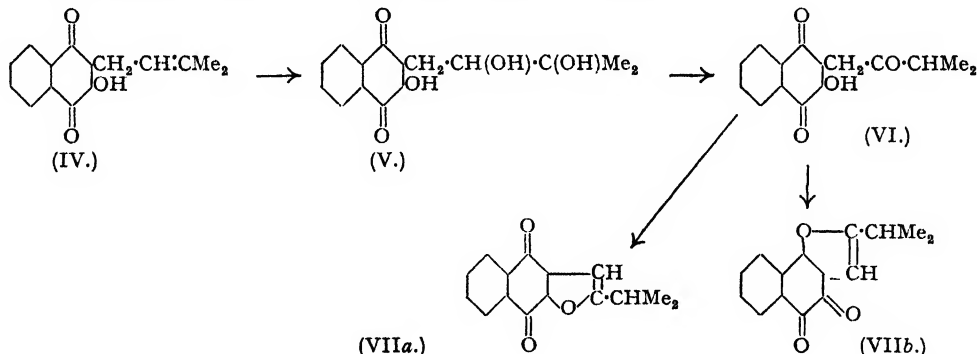
I. Hydroxydroserone. II. Javanicin. III. Anhydrojavanicin. IV. Oxyjavanicin.

These facts suggested then that javanicin was a dihydroxylated naphthaquinone carrying in addition to a β -methoxyl group a substituent which was able to undergo dehydration (cyclisation) by interaction with a neighbouring hydroxyl group. In view of the magnificent colour of javanicin in alkali and its acidity, the hydroxyls were believed to be in the *peri*-positions. Attempts were made to confirm this analytically by the formation of a boric acid complex (Macbeth and Winzor, *J.*, 1935, 334) but under conditions which precluded anhydride formation a stable complex proved unobtainable. That two hydroxyls were indeed present was shown by the behaviour of javanicin towards acylating agents under milder conditions than were used in the original experiments described above. When it was acetylated with acetic anhydride in pyridine diacetyljavanicin, $C_{18}H_{18}O_8$, was formed, and treatment with benzoyl chloride in pyridine afforded dibenzoyljavanicin, $C_{26}H_{26}O_8$. The acylation of a number of hydroxylated naphthaquinones has been described in the literature and no difficulty seems to have been encountered in fully acylating these compounds, so it was concluded that javanicin contained no more than two hydroxyl groups together with a β -methoxyl group.

On oxidation by the Kuhn-Roth method, javanicin gave two molecules of volatile fatty acid indicating two substituents, so the structure could be written in the form $C_{10}HO_2(OH)_2(OMe)RR'$, where $R + R' = C_4H_8O$. For the following reasons the four carbon atoms could only be distributed so that R contained C_1 and R' contained C_3 . The oxygen atom in the grouping C_4H_8O could not be placed on a terminal carbon atom for the side chain could not then have afforded a molecule of volatile fatty acid. If therefore there had been a

C_8, C_8 distribution the substituents would have been Et and COMe [or possibly $CH(OH)Me$], but these would not reasonably permit cyclisation. The remaining possibilities therefore for R, R' are Me and $CH_2 \cdot COMe$, or less likely, in view of the analytical results, Me and $CH_2 \cdot CH(OH)Me$. When javanicin was oxidised with sodium hypiodite or hypobromite, considerable yields of iodoform or bromoform were obtained. Moreover, when javanicin was treated with 2:4-dinitrophenylhydrazine a *mono-2:4-dinitrophenylhydrazone* was formed. Under the same conditions hydroxydroserone failed to react with dinitrophenylhydrazine and it was concluded that javanicin contained the substituents Me and $CH_2 \cdot COMe$. This conclusion was in agreement with the finding that javanicin had no observable optical activity, and that hydrogenation afforded no evidence of an ethylenic linkage. Catalytic hydrogenation resulted in rapid uptake of 1 mol. of hydrogen with disappearance of the colour, which was quickly regenerated in presence of air. From the recovered coloured solution the original pigment could be isolated, and obviously hydrogenation to this extent resulted only in formation of a leuco-compound. A second mol. of hydrogen was slowly absorbed, and further hydrogenation was very slow indeed; this stage corresponds supposedly to reduction of the ketone grouping followed by progressive reduction of the naphthalene nucleus, but no pure hydro-compounds were isolated. This suggested the partial structures (II) and (III) ($R = COMe$) for javanicin and its anhydromonoacetate respectively. These structures leave one unsubstituted position in the naphthalene nucleus; accordingly, after anhydrojavanicin was treated with bromine under very mild conditions a *monobromoanhydrojavanicin* was isolated. Furthermore, rather prolonged treatment of javanicin or anhydromonoacetyljavanicin with acetic anhydride gave an *acetoxo*-derivative of anhydroacetyljavanicin, $C_{18}H_{16}O_8$. Highly substituted naphthaquinones are known to undergo Thiele-Winter acetylation by this treatment, though with some difficulty.

The ready cyclodehydration of javanicin and its derivatives as pictured above is perhaps paralleled by the behaviour of lapachol (IV). Dihydroxylapachol (V) on dehydration gives, among other products, hydroxyisalapachol (VI), which on further dehydration affords two products formulated by Hooker (*J.*, 1896, 69, 1360) as (VIIa) and (VIIb).

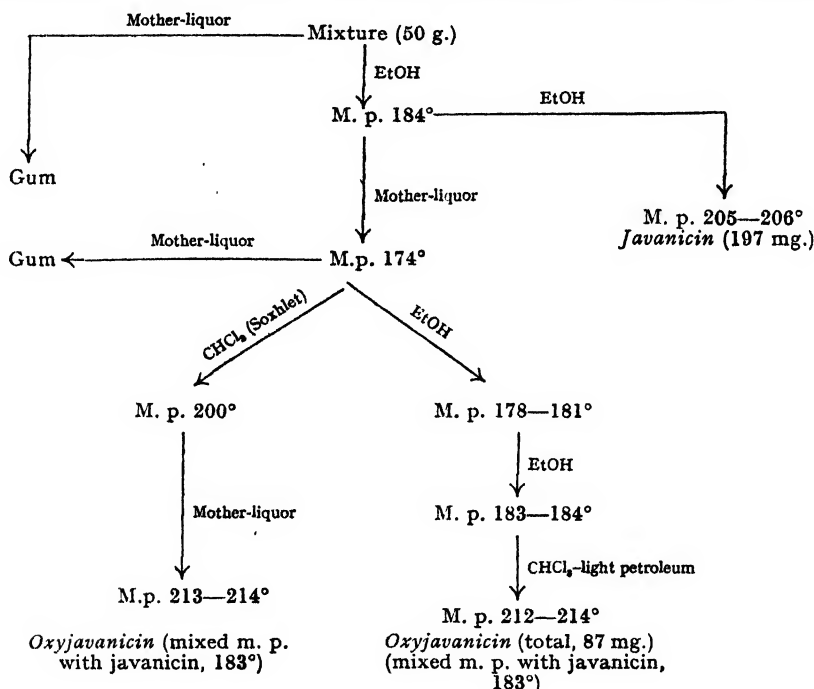


It may be pointed out that quinones of various kinds have been frequently observed to have strong antibacterial actions, and that the action of javanicin (and oxyjavanicin) is undoubtedly due in large measure to the quinone nature. Like that of other quinones, for example, its action is inhibited, though with some difficulty, by compounds containing thiol groupings. On the other hand, it seems equally certain that specific structural effects are exerted. Thus, comparison of javanicin with the nearly related hydroxydroserone showed that the activity of the latter especially towards *Myco. phlei* was surprisingly small (Arnstein, Cook, and Lacey, *Brit. J. Exp. Path.*, 1946, 27, 349).

EXPERIMENTAL.

Production of Javanicin and Oxyjavanicin.—Stock slope cultures of *F. javanicum* were grown on a medium containing Kepler's malt extract (3%) and agar (2%) in $6'' \times 1''$ test-tubes. The mycelium of a single slope was pulped with sterile water (50 c.c.), and the suspension (2—3 c.c.) used to inoculate bottles of liquid medium. This technique was adopted to ensure even and prompt growth. The liquid medium contained: Sodium nitrate, 20 g.; potassium chloride, 5 g.; anhydrous magnesium sulphate, 2.5 g.; dipotassium hydrogen phosphate, 10 g.; ferrous sulphate heptahydrate, 0.1 g.; glucose, 400 g.; "Bactotryptone" (Difco) or "Eupepton" (No. 2) (Allen and Hanbury, Ltd.), 50 g.; distilled water to 10 l. The inorganic salts were dissolved separately in small portions of hot distilled water and added to distilled water (ca. 8 l.). Glucose in water (1 l.) and bactotryptone or eupepton in water (500 c.c.) were

added, and the volume made up. The medium, which was at pH 6.8–7.0 without further adjustment was distributed into quart-size milk bottles, each containing 400 c.c., furnished with cotton-wool plugs and sterilised at 15 lb. for 15 minutes. The inoculated bottles were incubated, stacked in an almost horizontal position at 25–28° for 10–14 days. The mycelium covered the surface only sparsely; it was highly pigmented (red) from the beginning and the medium became distinctly red after about 7 days. The antibiotic activity and colour of the medium increased to a maximum after about 10 days, the medium then having pH 3. All bio-assays were carried out by the serial dilution method, as plate assays were unreliable, especially on partly purified material. Before assay the solutions were adjusted to pH 7 and sterilised by heat; Seitz filtration resulted in the pigment and antibacterial principles being retained on the filter. (a) In a typical batch the filtered metabolism solution (11 l.), which inhibited the growth of *Staph. aureus* at a dilution of 1:100, was extracted twice with ether (2.5 l.) previously freed from peroxides. The ethereal solution was twice extracted with saturated aqueous sodium hydrogen carbonate, which removed a mixture of apparently at least several antibacterially inactive pigment components. The remaining ethereal solution was extracted with *N*-sodium carbonate (4 × 500 c.c.), which removed all the activity. By adjusting the aqueous solution to pH 7 and again extracting with ether (2 l.), the activity and pigment were returned to the organic solvent. The dried ethereal solution was evaporated to 50 c.c., whereupon most of the pigment separated; the mother-liquor yielded only a small quantity of gummy solid, which was rejected. The solid pigment (0.509 g.) had m. p. ca. 168° and inhibited the growth of *Staph. aureus* at a dilution of 1:200,000. The mixture was crystallised according to the following scheme:



(b) In another batch of metabolism medium (20 l.) the mycelium was filtered off, yielding 31 g. of dry material after drying at 100° for several hours. The finely powdered mycelium (20 g.) was extracted (Soxhlet) with light petroleum for 6 hours, no more red pigment then appearing to be extracted. On concentration to small volume (50 c.c.) and cooling, a small quantity of red solid (20 mg.), m. p. 200°, was obtained. One recrystallisation from hot acetone-ethanol (1:1) (5 c.c.) afforded pure crystalline material (laths), m. p. 207° (decomp.) alone or mixed with javanicin obtained from the filtrate (see below). (c) The filtrate from (b) (20 l.) was extracted with ether-benzene (1:1) (4 l.). After being extracted once with saturated aqueous sodium hydrogen carbonate solution (1 l.) and washed with water (1 l.), the organic solvent was shaken with 1% sodium hydroxide (1 l.). The deep violet-purple aqueous layer was separated, and the pigment re-extracted into benzene (1 l.) by acidifying with 10% phosphoric acid. The benzene layer was washed once with water (500 c.c.), dried, and evaporated to dryness under reduced pressure. The solid residue was extracted (Soxhlet) with acetone-ethanol (1:1) (50 c.c.). On cooling, almost pure javanicin, m. p. 200° (450 mg.), separated. One recrystallisation from hot acetone-ethanol (1:1) (50 c.c.) yielded pure javanicin, m. p. 207–208° (decomp.). Method (c) was more convenient than (a) and gave consistent yields provided spore suspensions had been used for inoculating the medium. When inoculation was carried out by using a platinum loop, the yields were very variable, as shown below:

Vol. of filtered metabolism solution (l.)	20	20	20	40
Yield of pure pigment { Mg.	430	325	433	950
{ Mg./l.	21.5	16.3	21.7	23.8

Javanicin when crystallised repeatedly from ethanol separated in red laths with a coppery lustre, m. p. 207.5–208° (decomp.). Analyses were carried out on different samples from several batches [Found: C, 62.1, 62.9, 61.8, 62.0, 62.4, 61.7; H, 4.95, 5.11, 4.92, 5.04, 5.11, 4.90. OMe, 10.4; side-chain Me (Kuhn–Roth), 9.2; active H, 0.98. $C_{18}H_{14}O_8$ requires C, 62.1; H, 4.86; 1 OMe, 10.7; 2 Me, 10.3; 3 H, 1.03%]. Light absorption in ethanol: λ_{\max} 3030, 5050 Å., $\log \epsilon$ 3.97, 3.90; in chloroform, λ_{\max} 3070, 5100 Å., $\log \epsilon$ 3.99, 3.86. Optical activity: A solution of javanicin (24.5 mg.) in acetone (50 ml.) in a 1-dm. tube showed no observable rotation.

Oxyjavanicin separated from chloroform or chloroform–light petroleum in clusters of red needles with a coppery lustre, m. p. 213–214° (decomp.; preheated bath) (Found: C, 58.6, 58.5; H, 4.65, 4.60; OMe, 9.9; side-chain Me, 5.3; active H, 0.79. $C_{18}H_{14}O_8$ requires C, 58.5; H, 4.61; OMe, 10.1; 1 Me, 5.56; 2 H, 0.66%). Light absorption: in chloroform, λ_{\max} 3030, 5050 Å., $\log \epsilon$ 4.08, 3.96.

Monoacetylanhydrojavanicin.—(a) *From javanicin*. Javanicin (38 mg.) was dissolved in redistilled acetic anhydride (2.5 c.c.), and a trace of concentrated sulphuric acid added. There was an immediate darkening, and the mixture was heated at 100° for a few seconds till most of the red colour had disappeared, then poured into ice-cold distilled water (10 c.c.) and set aside for $\frac{1}{2}$ hour; a yellow solid separated (yield, after drying in a vacuum, 26.3 mg.), m. p. 229–238° (decomp.). After two recrystallisations from ethanol the product formed long needles, m. p. 247–248° (decomp.) [Found, on different samples: C, 64.3, 65.05; H, 4.7, 4.6; OMe, 8.2, 9.3; *M* (cryoscopic in camphor), 317. $C_{18}H_{14}O_8(OMe)$ requires C, 64.9; H, 4.6, OMe, 9.85%; *M*, 314]. Light absorption: in ethanol, λ_{\max} 2420, 2650, 3080, 3730 Å., $\log \epsilon$ 4.16, 4.20, 3.97, 3.59.

(b) *From anhydrojavanicin*. Anhydrojavanicin (29 mg.) was suspended in acetic anhydride (1 c.c.) containing a trace of concentrated sulphuric acid. On heating to 100° the colour changed to yellow. After 2 minutes the solution was poured on crushed ice (5 g.) and set aside for $\frac{1}{2}$ hour, the yellow product separating in clusters of needles (28 mg.). After one crystallisation from ethanol, the m. p. was 249–250° (decomp.) alone and when mixed with javanicin anhydromonoacetate obtained above.

Anhydrojavanicin.—Javanicin (200 mg.) was suspended in dry ether (250 c.c.). Saturated ethereal hydrogen chloride (250 c.c.) was added, followed by anhydrous zinc chloride (0.5 g.). The mixture was shaken in a stoppered bottle for 3 hours, the colour having then changed to orange. The ethereal solution was washed several times with water till free from acid. The aqueous layer was washed with benzene (3 × 150 c.c.) to remove all the pigment. The benzene layer was combined with the ethereal solution, again washed with water (2 × 100 c.c.), and dried (Na_2SO_4). After removal of solvent, the solid residue was crystallised twice from acetone, from which it separated in clusters of needles, m. p. 244–245° (decomp.) (Found: C, 66.4; H, 4.50; active H, 0.53. $C_{18}H_{12}O_8$ requires C, 66.2; H, 4.42; one active H, 0.37%). Light absorption: in ethanol, λ_{\max} 2300, 2640, 3160, 4500 Å., $\log \epsilon$ 4.49, 4.12, 3.95, 3.95. Javanicin (17 mg.) and concentrated sulphuric acid (1 c.c.) were heated together at 100° for 90 seconds. The solution was poured on crushed ice (10 g.), and a brown solid separated (20 mg.). The solid gave a violet coloration with 10% sodium hydroxide. It was dissolved in ethanol and reprecipitated by adding water, and then had m. p. 229–233° (decomp.). Repetition of this treatment yielded 1.3 mg. of a product which showed the following light absorption, in ethanol: λ_{\max} 2350, 3160, 3240, 4560 Å.; $\log \epsilon$ (calculated for *M* = 284) 4.61, 3.92, 3.92, 3.91.

Javanicin Leucoanhydrotriacetate.—Anhydrojavanicin (250 mg.) in pyridine (20 c.c.) was warmed with acetic anhydride (2.5 c.c.). Zinc dust (1 g.) was added, and the reaction allowed to proceed for 5 minutes, the supernatant liquid then having become pale yellow. The solution was filtered and evaporated to small bulk. After a short time an almost colourless solid separated in rhombic prisms, m. p. 256–257° (decomp.) (321 mg., 87%). One recrystallisation from acetone–benzene afforded the pure *leucoanhydrotriacetate*, m. p. 258° (decomp.) (Found: C, 63.05; H, 5.10; CH_3CO , 34.1. $C_{22}H_{20}O_8$ requires C, 63.0; H, 5.0; CH_3CO , 32.25%). Light absorption in dioxan: λ_{\max} 2610 Å., $\log \epsilon$ 4.92. Optical activity: A solution of 17.3 mg. in 2 ml. of chloroform in a 1-dm. tube showed no observable rotation.

Diacetyljavanicin.—Javanicin (50 mg.) was dissolved in pyridine (3 c.c.) and mixed with acetic anhydride (0.2 c.c.) in pyridine (2 c.c.). The solution was heated at 70° for 1 hour and kept at room temperature for a further 48 hours. After concentration to 1 c.c., a little ice was added which precipitated some gummy material. The supernatant liquid was decanted and further diluted with water (10 c.c.) and a yellow solid separated on cooling. The solid was crystallised from ethanol containing a little acetone. A second crystallisation from aqueous acetone yielded the pure *compound* (6.5 mg.) in clusters of needles, m. p. 207–208° (decomp.) (Found: C, 61.05; H, 4.95. $C_{18}H_{14}O_8$ requires C, 61.0; H, 4.81%). Light absorption, in ethanol: λ_{\max} 2210, 2900, 4260 Å., $\log \epsilon$ 4.57, 4.17, 3.79.

Dibenzoyl javanicin.—Javanicin (70 mg.), dissolved in pyridine (4 c.c.), was treated with benzoyl chloride (250 mg.). After about 10 minutes the red colour of the solution had changed to yellow. After a further 16 hours at room temperature, the solution was evaporated to dryness and the solid residue dissolved in ether–benzene (1 : 1) (25 c.c.). The solution was well washed with dilute hydrochloric acid (3 × 20 c.c.), followed by saturated aqueous sodium hydrogen carbonate (3 × 20 c.c.) and distilled water (20 c.c.). After drying (Na_2SO_4) the solvent was evaporated. The yellow residue was dissolved in ethanol (5 c.c.). On dilution with water (15 c.c.) some crystallisation took place, but most of the material was precipitated as a gum. On washing with cold ethanol, a pale yellow solid (47 mg.) was obtained. The *product* crystallised from hot ethanol–acetone (1 : 1) in bunches of needles, m. p. 216–217° (decomp.; preheated bath) (Found: C, 69.8; H, 4.41. $C_{20}H_{18}O_8$ requires C, 69.9; H, 4.42%). Light absorption in ethanol: λ_{\max} 2290, 2600, 3650 Å., $\log \epsilon$ 4.63, 4.44, 3.52. Optical activity: A solution of 6.7 mg. in 2 ml. of chloroform in a 1-dm. tube showed no observable rotation.

Javanicin (29 mg.) was dissolved in *N*-sodium hydroxide (5 c.c.) and treated with sufficient iodine in potassium iodide to decolorise the solution completely. The solution had a strong smell of iodoform, and after standing at 0° overnight the precipitated iodoform was collected and dried (P_2O_5); yield 12.6 mg., m. p. 121–122° (decomp.) alone and when mixed with authentic iodoform.

Javanicin Mono-2 : 4-dinitrophenylhydrazine.—A hot solution of javanicin (25 mg.) in ethanol (3 c.c.) and ethyl acetate (1 c.c.) was added to a cold solution of 2 : 4-dinitrophenylhydrazine, prepared by warming 2 : 4-dinitrophenylhydrazine (50 mg., 3 equivs.) with concentrated sulphuric acid (0.1 c.c.) till completely

dissolved, and diluting the cold solution with ethanol (1 c.c.). A red solid was immediately precipitated. The solution was warmed (100°) for a few seconds and cooled in ice. The solid was filtered off; yield 34 mg. (82%), m. p. 252—254° (decomp.; darkening at 249°). Recrystallisation from pyridine by adding ethanol yielded pure *javanicin mono-2:4-dinitrophenylhydrazone*, separating in needles, m. p. 255—256° (decomp.) (Found: C, 54.2, 53.4; H, 3.9, 3.7; N, 11.9. $C_{21}H_{11}O_8N_4$ requires C, 53.6; H, 3.83; N, 11.9%).

Monobromoanhydrojavanicin.—Anhydrojavanicin (50 mg.) was dissolved in chloroform (10 c.c.) and treated with excess of bromine in chloroform. The mixture was kept for 20 minutes at room temperature and evaporated to dryness. After being washed with a little ethanol, the residual solid was crystallised from benzene, from which it separated as tapered laths, m. p. 259—260° (decomp.) (yield 14 mg.). One recrystallisation from benzene-ethanol gave the pure *product*, m. p. 259—260° (decomp.) (Found: C, 51.35; H, 3.76. $C_{18}H_{11}O_8Br$ requires C, 51.3; H, 3.14%).

Acetoxyanhydroacetyljavanicin.—Javanicin (50 mg.) was refluxed for 15 minutes with acetic anhydride (5 c.c.) and anhydrous sodium acetate (50 mg.). The solution was poured on crushed ice, and the yellow solid filtered off after $\frac{1}{2}$ hour. The solid was dissolved in acetone and reprecipitated with water; yield 14 mg. One recrystallisation from acetone-ethanol afforded the pure *compound*, m. p. 265° (extensive decomp.; darkening at 250°) (Found: C, 63.6; H, 4.8. $C_{18}H_{14}O_7$ requires C, 64.0; H, 4.5%).

We thank Sir Ian M. Heilbron, D.S.O., F.R.S., for his interest and encouragement, Dr. M. S. Lacey for bacteriological results, and the Medical Research Council and Rockefeller Foundation for financial assistance.

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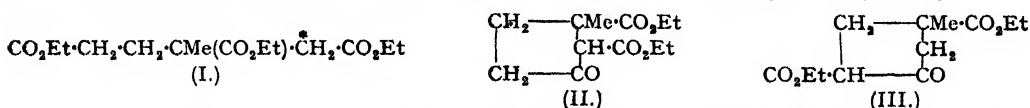
[Received, October 3rd, 1946.]

190. The Course of Cyclisation in the Formation of Alicyclic Rings. Part I. Effect of Alkyl Groups on the Cyclisation of Esters of Polycarboxylic Acids.

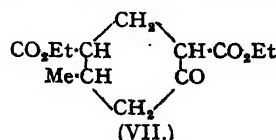
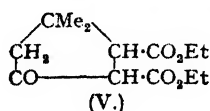
By R. N. CHAKRAVARTI.

The Dieckmann condensation of a simple or substituted β -alkyl-adipic or -pimelic ester leads to a ketonic ester in which the reactive methylene group nearer to the alkyl radical remains unaffected by preference when there is an alternative way of ring formation.

A DIFFICULTY often experienced in the synthesis of hydroaromatic ring systems is the determination of the structure of the ketonic esters obtained by the sodium condensation of esters of unsymmetrical polycarboxylic acids having two reactive methylene groups. A well-known example of this type is afforded by the sodium condensation of ethyl 2-methylbutane-1:2:4-tricarboxylate (I), which, on the basis of certain oxidative degradations, was found to lead to the keto-ester (II) (Baker, *J.*, 1931, 1548; cf. Banerjee, *J. Indian Chem. Soc.*, 1940, 17, 423). More critical examination, however, revealed that the product of the condensation should be represented as ethyl 4-methylcyclopentanone-2:4-dicarboxylate (III) (Chakravarti, *J. Indian Chem. Soc.*, 1943, 20, 173, 189, 243, 247, 399), and not (II) as was found by Baker (*loc. cit.*).



The cyclisation of the analogously constituted ethyl 2:2-dimethylbutane-1:3:4-tricarboxylate (IV) led to the keto-ester (V) (Perkin and Thorpe, *J.*, 1906, 89, 781). Also, only (VII) was isolated in the cyclisation of ethyl 2-methylpentane-1:3:5-tricarboxylate (VI) (Chakravarti, *J. Indian Chem. Soc.*, 1944, 21, 322).*

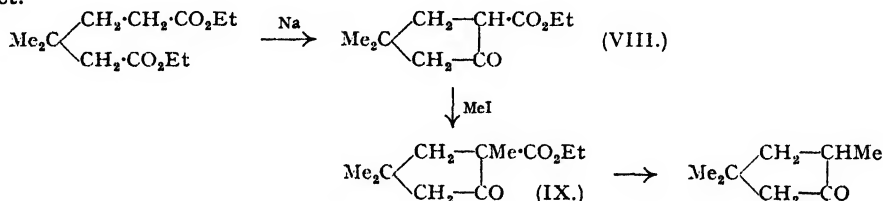


The above results definitely lead one to believe that the methyl groups in (I), (IV), and (VI) exert some steric influence on the reactive methylene groups marked (*), which accounts for

* Since this paper was communicated, another interesting case has been discussed elsewhere (Chakravarti, *Experientia*, 1947, 3, 149).

their lesser reactivity. This effect may be due to the positive character of the alkyl group, and if this be true it can be concluded that the positive character of a methyl group is much more pronounced than the negative character of a carbethoxyl group (cf. the first example cited above).

In the present instance, while devising a suitable method for the synthesis of 4:4-dimethylcyclopentanone-2-acetic acid required in connection with another work, it became necessary to investigate the action of sodium on ethyl $\beta\beta$ -dimethyladipate. For this purpose, the product of the sodium condensation was heated with excess of methyl iodide and the resulting methylated keto-ester hydrolysed with dilute aqueous alkali to give a neutral ketone, b. p. 160°. It gave a crystalline semicarbazone, m. p. 168°, which proved to be identical with that of 2:4:4-trimethylcyclopentanone (Wallach, *Annalen*, 1918, 414, 331; Qudrat-i-Khuda, *Nature*, 1933, 132, 210; Dey and Linstead, *J.*, 1935, 1063). No evidence of the presence, in the hydrolysed product, of the isomeric ketone, 2:3:3-trimethylcyclopentanone (von Kregten, *Rec. Trav. chim.*, 36, 78; Noyes, *Ber.*, 1899, 32, 2291), b. p. 167–169° (semicarbazone, m. p. 222°), could be detected, thus indicating that in this cyclisation the keto-ester (VIII) is the only product.



The result obtained above confirms the view already postulated that the reactivity of a methylene group is reduced considerably by its closer proximity to a methyl group (or any other alkyl group). Thus the action of sodium on the ester of a substituted β -alkyl-adipic or -pimelic acid (having two alternatives for cyclisation) may be expected to lead to a ketonic ester in which the reactive methylene group, nearer to the alkyl radical, remains unaffected by preference. The other isomer in such a case, if produced at all, can only be in much smaller amount. This view is also in line with the results obtained by the cyclisation of ethyl β -methyl-adipate (Dieckmann and Groeneveld, *Ber.*, 1900, 33, 595) and -pimelate (Einhorn and Klages, *ibid.*, 1901, 34, 3793).

EXPERIMENTAL.

$\beta\beta$ -Dimethyladipic acid, required for this work, was prepared by the improved method of Rydon (*J.*, 1936, 594; 1937, 1341).

Ethyl 2:4:4-Trimethylcyclopentanone-2-carboxylate (IX).—Ethyl $\beta\beta$ -dimethyladipate (20 g.) was heated on the water-bath with a fine suspension of sodium (3.9 g.) in anhydrous benzene (50 c.c.). The heating was continued for about 6 hours till the whole of the sodium had passed into solution. The product was then cooled in ice, treated with excess of methyl iodide (20 c.c.), and kept overnight. The methylation was completed by heating the reaction mixture on the water-bath for 5–6 hours. The product at this stage should not give any coloration with alcoholic ferric chloride. Sufficient water was added to dissolve the sodium iodide, and the benzene layer was separated. It was washed thoroughly with water and dried (CaCl_2), and the solvent evaporated. The residual liquid on distillation under reduced pressure gave the ester as a colourless mobile oil (12 g.) with a characteristic odour, b. p. 88°/4 mm. (Found: C, 66.5; H, 9.1. $\text{C}_{11}\text{H}_{18}\text{O}_3$ requires C, 66.7; H, 9.1%).

2:4:4-Trimethylcyclopentanone.—The above ketonic ester (11.5 g.) was heated on a sand-bath for 6 hours with a solution of potassium hydroxide (12 g.) in water (150 c.c.). When cold, the product was taken up in ether, washed well with water, and dried (Na_2SO_4), and the ether removed. The liquid remaining was then distilled; with the exception of a little high boiling residue, it came over constantly at 160°, as a colourless liquid (6.8 g.) with a peppermint-like smell (Found: C, 75.9; H, 11.2. Calc. for $\text{C}_8\text{H}_{14}\text{O}$: C, 76.2; H, 11.1%). With semicarbazide acetate in aqueous alcohol it readily gave a semicarbazone, which crystallised from spirit in colourless shining laminae, m. p. 168°, undepressed in admixture with an authentic specimen of the semicarbazone of 2:4:4-trimethylcyclopentanone (Found: C, 59.2; H, 9.4. Calc. for $\text{C}_8\text{H}_{11}\text{ON}_3$: C, 59.0; H, 9.3%).

Further work with 4:4-dimethylcyclopentanone-2-acetic acid is in progress.

My best thanks are due to Prof. J. C. Bardhan for encouragement and to Mr. J. Chakraverti for facilities.

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[Received, November 14th, 1946.]

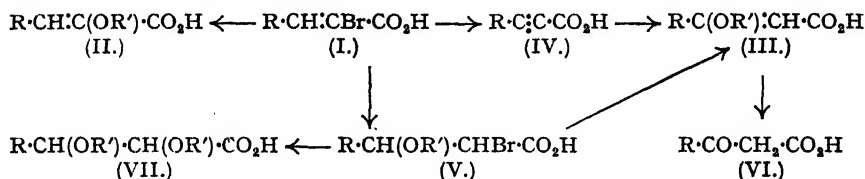
191. Olefinic Acids. Part II. The Reactivity of α -Bromoacrylic Acid and Some Related Compounds.

By L. N. OWEN and H. M. BABATUNDE SOMADE.

α -Bromoacrylic acid reacts with alkoxides to give α -bromo- β -alkoxy-propionic acids which, by further action, are converted into β -alkoxy-acrylic and $\alpha\beta$ -dialkoxy-propionic acids, the proportion of β -alkoxy-acid being greater when the higher alkoxides are used. In contrast with the results obtained in the crotonic series (Part I), no α -alkoxy-acrylic acids are formed. Towards thioacetic acid, benzylthiol, diazomethane, and methyl diazoacetate, the order of decreasing reactivity is, as would be anticipated, α -bromoacrylic acid, α -bromocrotonic acid, α -bromo- $\beta\beta$ -dimethylacrylic acid; the products obtained by these addition reactions have been investigated and identified.

The absorption spectra of several α - and β -alkoxy-acrylic acids are recorded.

THE investigations described in Part I (Owen, *J.*, 1945, 385) established that α -bromocrotonic acid (I; R = Me) reacted with alkoxides (or the appropriate alcoholic alkali) to give α - and β -alkoxy-crotonic acids, (II; R = Me) and (III; R = Me), the proportion of the latter being greater with the higher alkoxides, but attempts to isolate either of the possible intermediates (IV) or (V) were unsuccessful.



Baker (*J.*, 1942, 520) in the course of attempts to prepare α -alkoxy-acrylic acids, has shown that $\alpha\beta$ -dibromopropionic acid, on treatment with boiling methanolic sodium methoxide, yields $\alpha\beta$ -dimethoxypropionic acid, not by direct substitution, but probably *via* α -bromoacrylic acid. The presence of other products was indicated by the unsaturated nature of the crude halogen-free acids isolated from the reaction mixture, but these were not identified, and the exact mechanism of the reaction was not established. It has now been found that β -methoxyacrylic acid is formed under these conditions; on cold acid hydrolysis it gives malonic semi-aldehyde (VI; R = H) (2:4-dinitrophenylhydrazone, m. p. 136°).

The reaction has been more closely studied by using α -bromoacrylic acid (I; R = H) as starting material, particularly with a view to comparing its behaviour with that of α -bromocrotonic acid. When boiled with methanolic sodium methoxide for 3 hours, the main product was α -bromo- β -methoxypropionic acid (V; R = H, R' = Me), which was isolated as its methyl ester, purified from unsaturated compounds by cautious treatment with aqueous permanganate, and characterised as the amide, m. p. 83°. The presence also of a small amount of β -methoxyacrylic acid (III; R = H, R' = Me) was demonstrated by the formation of malonic semi-aldehyde by acid hydrolysis of a portion of the reaction products. No α -methoxyacrylic acid could be detected, but, clearly, if it had been formed it might well have been converted by subsequent reaction with methanol into $\alpha\beta$ -dimethoxypropionic acid. This, however, has been shown not to be the case, since, by saponification of methyl α -methoxyacrylate, crystalline α -methoxyacrylic acid, m. p. 52°, was obtained,* which was recovered unchanged after treatment with boiling methanolic sodium methoxide; β -methoxyacrylic acid, treated similarly, was likewise unaffected.

It is evident, therefore, that α -bromoacrylic acid, in marked contrast to α -bromocrotonic acid, undergoes addition, rather than substitution, and gives the bromomethoxy-acid (V; R = H, R' = Me), the bromine atom in which is then either eliminated as hydrogen bromide, forming β -methoxyacrylic acid (III; R = H, R' = Me), or replaced to give $\alpha\beta$ -dimethoxypropionic acid (VII; R = H, R' = Me).

It was not possible to interrupt the reaction of α -bromoacrylic acid with ethanolic alkali at the bromo-ethoxy-acid stage, probably owing to the heterogeneous nature of the reaction mixture resulting from the reduced solubility of the salts in ethanol, but on taking the reaction to com-

* Allpress and Haworth (*J.*, 1924, 125, 1233) tentatively ascribed this structure to an unsaturated liquid acid, b. p. 65–75°/12 mm., obtained by the action of methyl chloroformate on fructose; it is possible that their product was an impure form of α -methoxyacrylic acid, although no other properties were given in support of the proposed constitution.

pletion β -ethoxyacrylic acid was obtained, together with $\alpha\beta$ -diethoxypropionic acid, isolated as the *ethyl* ester. Treatment of α -bromoacrylic acid with potassium *isopropoxide* gave a liquid product, containing 88% of β -*isopropoxyacrylic acid* with 12% of $\alpha\beta$ -*diisopropoxypropionic acid*, which could not be separated, whilst with potassium *tert.*-butoxide the only product isolated was crystalline β -*tert.*-*butoxyacrylic acid*. This progressive increase in the proportion of the β -alkoxy-acid as the higher alkoxides are used is similar to that observed in the case of α -bromocrotonic acid; in the present reactions, however, the increase is at the expense of dialkoxypropionic acid, whilst in the crotonic series it is accompanied by a diminution in the amount of α -alkoxy-acid.

The absorption data for the α - and β -alkoxy-acrylic acids are shown in the table. As was observed in the crotonic series (Owen, *loc. cit.*) the β -compounds absorb more strongly than their α -isomerides, but in contrast, not at appreciably different wave-lengths.

Light Absorption of Alkoxy-acrylic Acids in Alcohol.

	$\lambda_{\max.}, \text{\AA.}$	$\epsilon_{\max.}$		$\lambda_{\max.}, \text{\AA.}$	$\epsilon_{\max.}$
α -Methoxy	2280	6000	β -Methoxy	2280	14,100
α -Ethoxy *	2290	7000	β -Ethoxy	2300	14,700
	2360 †	6150			
			β - <i>iso</i> Propoxy	2340	14,000 †
			β - <i>tert.</i> -Butoxy	2370	15,400

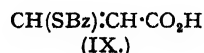
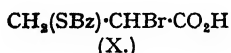
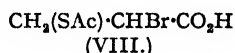
* M. p. 61°, prepared by the method of Claisen (*Ber.*, 1898, **31**, 1019; cf. von Auwers, *ibid.*, 1911, **44**, 3524).

† Inflection.

‡ Corrected value.

The greater ease of addition to α -halogeno-acrylic, as compared with α -halogeno-crotonic, acids has also been demonstrated in their reactions with a number of other reagents. α -Bromoacrylic acid reacted readily with thioacetic acid to give α -bromo- β -(*acetylthio*)propionic acid (VIII); the corresponding *chloro*-acid was obtained similarly. α -Bromocrotonic acid failed to undergo addition of the reagent, thus indicating that diminution of ethenoid activity is brought about not only by the methyl group in the β -position, but also by the halogen atom, since crotonic acid undergoes the reaction (Holmberg and Schjanberg, *Arkiv Kemi, Min. Geol.*, 1940, **14** A, No. 7, 22).

With benzylthiol in pyridine solution, α -bromoacrylic acid gave β -(*benzylthio*)acrylic acid (IX), presumably *via* the intermediate compound (X); α -bromocrotonic acid could not be induced to react with the reagent.

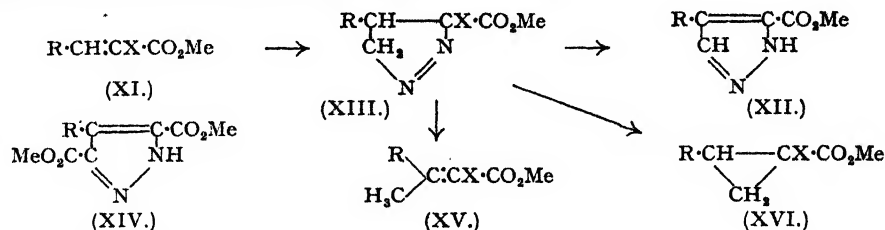


Auwers and König (*Annalen*, 1932, **496**, 31) reported that methyl α -chlorocrotonate (XI; R = Me, X = Cl) reacted with diazomethane to give methyl 4-methylpyrazole-3-carboxylate (XII; R = Me), hydrogen chloride being spontaneously evolved by the unstable intermediate (XIII; R = Me, X = Cl). It has now been shown that α -chloro- and α -bromoacrylic acids, on treatment with diazomethane, give methyl pyrazole-3-carboxylate (XII; R = H), whilst α -bromocrotonic acid gives (XII; R = Me). α -Bromo- $\beta\beta$ -dimethylacrylic acid, on the contrary, was merely converted into its *methyl* ester (*amide*, m. p. 129°) and did not undergo addition, the extra methyl group in the β -position being sufficient to inhibit the reaction.

Buchner and Papandieck (*Annalen*, 1893, **273**, 246), by treatment of methyl $\alpha\beta$ -dibromopropionate with methyl diazoacetate, obtained dimethyl pyrazole-3 : 5-dicarboxylate (XIV; R = H), but did not isolate any of the intermediates. Both methyl α -bromo- and α -chloroacrylate have now been found to give this product under these conditions, whilst methyl α -bromo- and α -chloro-crotonates reacted much less readily, and gave a small yield of *methyl* 4-methylpyrazole-3 : 5-dicarboxylate (XIV; R = Me). Methyl α -bromo- $\beta\beta$ -dimethylacrylate was unaffected by methyl diazoacetate.

In the reaction of diazomethane with α -substituted acrylic or crotonic esters (XI), provided that the intermediate pyrazoline (XIII) does not tend to lose HX and form pyrazoles (cf. above), it may lose nitrogen to give either a higher homologue (XV) of the ester (XI) or a cyclopropane derivative (XVI). The composition of the product depends on the nature of the substituent X; if it is methyl, both (XV) and (XVI) are obtained, whilst if X is a cyano- or carbalkoxy-group the sole product is (XV) (Auwers and König, *Annalen*, 1932, **496**, 252; Young, Andrews, Lindenbaum, and Cristol, *J. Amer. Chem. Soc.*, 1944, **66**, 810). It was therefore not unexpected to find that methyl α -methoxyacrylate (XI; R = H, X = OMe) on reaction with diazomethane

gave a product which contained methyl 1-methoxycyclopropane-1-carboxylate (XVI; R = H, X = OMe), characterised as the *amide*, m. p. 117°. This +T effect of the methoxyl group in the α -position was also shown by the observation that although, as mentioned above, methyl α -methoxyacrylate was unaffected by methanolic sodium methoxide, it reacted with methanolic hydrogen chloride to give methyl α -dimethoxypropionate.



EXPERIMENTAL.

Action of Sodium Methoxide on $\alpha\beta$ -Dibromopropionic Acid.—To the acid (24 g.) in warm methanol (20 c.c.) was added methanolic sodium methoxide (110 c.c., 3.76 N). After the vigorous reaction had subsided, the mixture was refluxed for 7 hours, during which the suspension of potassium α -bromoacrylate disappeared and was replaced by a granular precipitate of potassium bromide. After removal of solvent, the residue was dissolved in water and acidified with hydrochloric acid, with ice-cooling. Extraction with ether gave a syrup, which partly crystallised on standing. The solid β -methoxyacrylic acid (1.1 g.) was dried on porous tile; it recrystallised from water in plates, m. p. 102° (Found: C, 47.2; H, 5.9; equiv., 102. $\text{C}_4\text{H}_6\text{O}_3$ requires C, 47.1; H, 5.9%; equiv., 102). Light absorption: see Table. On treatment with a cold solution of 2:4-dinitrophenylhydrazine sulphate in 5N-sulphuric acid for 2 hours it gave the 2:4-dinitrophenylhydrazone of malonic semi-aldehyde, which crystallised from warm ethyl acetate-light petroleum (b. p. 40–60°) in lemon-yellow nodules, m. p. 136° (decomp.), and gave a deep red solution in aqueous sodium hydroxide (Found: C, 40.0; H, 3.3; N, 20.6. $\text{C}_8\text{H}_6\text{O}_8\text{N}_4$ requires C, 40.3; H, 3.0; N, 20.9%).

α -Bromoacrylic Acid.— $\alpha\beta$ -Dibromopropionic acid (90 g.) was dissolved in water and neutralised with N-sodium hydroxide at 0°. An equal volume of N-sodium hydroxide was then added and the solution left at room temperature for 1 hour. After acidification with a slight excess of concentrated hydrochloric acid (Congo-red), ether extraction yielded α -bromoacrylic acid, which after recrystallisation from light petroleum (b. p. 60–80°) formed colourless prisms (51 g., 87%), m. p. 72° (lit. 70°). This improved procedure gives a product which, unlike less pure material, shows no sign of decomposition after being kept for several months.

Reaction of α -Bromoacrylic Acid with Alkoxides.—(i) A solution of the acid (15 g.) in methanol (40 c.c.) was treated with methanolic sodium methoxide (35 c.c., 3.67N) and refluxed for 3 hours, after which it was evaporated to dryness, and the residue dissolved in water, acidified with hydrochloric acid, and extracted with ether. The liquid acid so obtained contained a small amount of β -methoxyacrylic acid, since a portion, on treatment with aqueous 2:4-dinitrophenylhydrazine sulphate, gave the 2:4-dinitrophenylhydrazone of malonic semi-aldehyde, m. p. 135°. The remainder (7 g.) was dissolved in methyl iodide (5 c.c.) and diluted with ether (10 c.c.), and silver oxide (15 g.) was added in small portions during $\frac{1}{2}$ hour. After refluxing for $\frac{1}{2}$ hour, the solution was filtered and evaporated to an oil, which on distillation furnished a main fraction (6.1 g.), b. p. 70–78°/15 mm. This was unsaturated towards alkaline permanganate, and gave a positive reaction on standing with aqueous 2:4-dinitrophenylhydrazine sulphate. It was therefore suspended in dilute sodium carbonate solution and treated with a slight excess of 2% aqueous potassium permanganate at 0°, with vigorous stirring. The recovered saturated ester (3.0 g.), b. p. 78°/15 mm., n_D^{20} 1.4510, was mainly methyl α -bromo- β -methoxypropionate, probably containing a small amount of methyl $\alpha\beta$ -dimethoxypropionate (Found: C, 33.4; H, 5.7. Calc. for $\text{C}_5\text{H}_8\text{O}_3\text{Br}$: C, 30.5; H, 4.6. Calc. for $\text{C}_6\text{H}_{10}\text{O}_4$: C, 48.6; H, 8.2%). On treatment with aqueous ammonia (d 0.880) it gave α -bromo- β -methoxypropionamide, m. p. 83° (Found: C, 26.2; H, 4.5. Calc. for $\text{C}_4\text{H}_8\text{O}_3\text{NBr}$: C, 26.4; H, 4.4%).

(ii) Ethanolic sodium ethoxide (45 c.c., 2N) was added to α -bromoacrylic acid (10 g.) in ethanol (10 c.c.) and the mixture was refluxed for 20 hours. The residue, after removal of solvent, was dissolved in water and acidified with hydrochloric acid, precipitating β -ethoxyacrylic acid (1.0 g.), which crystallised from warm water in plates, m. p. 109°. Light absorption: see Table. Ether extraction of the residual aqueous portion gave a liquid halogen-free acid (5.1 g.), which was esterified in the usual way in ethereal solution with ethyl iodide and silver oxide. The crude ester was then purified by treatment with 2% potassium permanganate, as already described, and on distillation gave methyl $\alpha\beta$ -diethoxypropionate (1.5 g.), b. p. 87°/11 mm., n_D^{20} 1.4130 (Found: C, 56.8; H, 9.8. $\text{C}_6\text{H}_{10}\text{O}_4$ requires C, 56.8; H, 9.5%).

(iii) α -Bromoacrylic acid (7.5 g.), dissolved in isopropanol (60 c.c.), was treated with a solution of potassium (5 g.) in isopropanol (60 c.c.), and the semi-solid mass was refluxed for 24 hours on the steam-bath. The solvent was then removed, and the residue dissolved in water and acidified with hydrochloric acid; an oil separated, but since it could not be induced to crystallise, the whole was extracted with ether. The liquid acid so obtained (7 g.), b. p. 55°/0.001 mm., n_D^{20} 1.4425, contained no halogen and was highly unsaturated. Light absorption: λ_{max} 2340 Å. (ϵ 12,300) (Found: equiv., 137. $\text{C}_5\text{H}_8\text{O}_3$ requires equiv., 130. $\text{C}_6\text{H}_{10}\text{O}_4$ requires equiv., 190). On treatment with aqueous 2:4-dinitrophenylhydrazine sulphate it gave the 2:4-dinitrophenylhydrazone of malonic semi-aldehyde, m. p. 129° (decomp.) after recrystallisation from dioxan, and was therefore mainly β -isopropoxyacrylic acid, probably containing

ca. 12% α -diisopropoxyacrylic acid. Attempts to isolate either component in a pure state were unsuccessful.

(iv) To a warm solution of potassium (10 g.) in *tert.*-butanol (200 c.c.) was added α -bromoacrylic acid (15.2 g.) in *tert.*-butanol (20 c.c.), and the semi-solid mass refluxed for 24 hours on the steam-bath. Water (100 c.c.) was then added and the *tert.*-butanol removed under reduced pressure. The residual aqueous solution was acidified to Congo-red with hydrochloric acid, which precipitated β -*tert.*-butoxyacrylic acid (3.2 g.); this was collected, and a further quantity (1.7 g.) obtained by extraction of the filtrate with ether. On recrystallisation from light petroleum (b. p. 60–80°) it formed long flat needles, m. p. 86.5° (Found: C, 58.6; H, 8.5; equiv., 144. $C_7H_{12}O_3$ requires C, 58.3; H, 8.4%; equiv., 144). Light absorption: see Table. On standing with aqueous 2:4-dinitrophenylhydrazine sulphate it gave the 2:4-dinitrophenylhydrazone of malonic semi-aldehyde, m. p. 131°. No other acidic products could be detected.

α -Methoxyacrylic Acid.—Methyl α -methoxyacrylate, b. p. 58–60°/15 mm., λ_{\max} . 2280 Å. (ϵ 7300), λ_{\min} . 2360 Å. (ϵ 6400), was prepared by the method of Baker (*loc. cit.*). The ester (2.1 g.) was heated at 100° with aqueous sodium hydroxide (15 c.c., 2N) for 1½ hours, and the solution then cooled, acidified with 2N-hydrochloric acid (15 c.c.), and extracted with ether. Evaporation of the dried extract gave α -methoxyacrylic acid (1.2 g.), which crystallised from light petroleum (b. p. 40–60°) in needles, m. p. 52° (Found: C, 46.8; H, 5.7. $C_4H_6O_3$ requires C, 47.0; H, 5.9%). Light absorption: see Table. On standing with aqueous 2:4-dinitrophenylhydrazine sulphate it gave the 2:4-dinitrophenylhydrazone of pyruvic acid, m. p. 218°.

Action of Sodium Methoxide on α -Methoxy- and β -Ethoxy-acrylic Acids.— α -Methoxyacrylic acid (0.2 g.) was refluxed with methanolic sodium methoxide (3 c.c., N) for 6 hours. After evaporation, acidification of the residue with hydrochloric acid and extraction with ether, the acid (0.17 g.), m. p. and mixed m. p. 50°, was recovered unchanged. β -Ethoxyacrylic acid (0.25 g.), treated similarly, was also recovered (0.21 g.), m. p. and mixed m. p. 108°.

α -Bromo- β -(acetylthio)propionic Acid.— α -Bromoacrylic acid (5 g.) was added in small portions to thioacetic acid (5 c.c.) in a flask cooled in ice. After the vigorous reaction had subsided, the solution was heated on the steam-bath for 15 minutes, and the excess of thioacetic acid then removed under reduced pressure. The solid acid obtained on cooling was recrystallised from carbon tetrachloride, from which it formed colourless prisms (6.9 g.), m. p. 85–86° (Found: C, 26.1; H, 3.2. $C_5H_6O_3SBr$ requires C, 26.4; H, 3.1%). Similar treatment of α -chloroacrylic acid (2 g.) afforded α -chloro- β -(acetylthio)propionic acid (3 g.), m. p. 75°, after recrystallisation from carbon tetrachloride (Found: C, 32.8; H, 3.75. $C_5H_6O_3ClS$ requires C, 32.9; H, 3.9%). Under the same conditions, α -bromocrotonic acid was recovered unchanged.

Action of Benzylthiol on α -Bromoacrylic Acid.—The acid (0.5 g.), pyridine (0.5 c.c.), and benzylthiol (1 c.c.) were heated on a steam-bath for 15 minutes. The solid which separated on cooling was freed from adhering oil on porous tile, dissolved in dilute hydrochloric acid, and extracted with ether. Removal of solvent yielded β -(benzylthio)acrylic acid, which crystallised from carbon tetrachloride in colourless plates, m. p. 162–163° (Found: C, 61.45; H, 5.3. $C_{10}H_{10}O_2S$ requires C, 61.8; H, 5.2%). Light absorption: λ_{\max} . 2740 Å. (ϵ 15,500). Similar experiments, in which traces of hydrochloric acid or benzoyl peroxide were used in place of pyridine, resulted only in the recovery of unchanged bromo-acid.

Reactions of α -Halogeno- α -olefinic Acids with Diazomethane.—(i) α -Bromoacrylic acid (2 g.) was dissolved in excess of ethereal diazomethane and left at 20° for 5 days. After removal of solvent, the liquid residue was warmed to 60°, whereupon there was a vigorous evolution of hydrogen bromide and the formation of methyl pyrazole-3-carboxylate, which crystallised from water in colourless prisms (0.9 g.), m. p. 141° (Found: C, 47.6; H, 4.7; N, 22.3. Calc. for $C_5H_6O_2N_2$: C, 47.6; H, 4.8; N, 22.2%). α -Chloroacrylic acid under identical conditions gave the same product, m. p. 141°.

(ii) α -Bromocrotonic acid (1 g.) treated similarly, gave methyl 4-methylpyrazole-3-carboxylate (0.51 g.), colourless prisms from water, m. p. 170° (Found: C, 51.2; H, 5.75; N, 19.8. Calc. for $C_6H_8O_2N_2$: C, 51.05; H, 5.7; N, 19.85%).

(iii) α -Bromo- β -dimethylacrylic acid (2 g.) was dissolved in excess of ethereal diazomethane and the solution kept at 20° for 12 days. Removal of solvent afforded a nitrogen-free product (1.8 g.), b. p. 98°/33 mm., which was identical with methyl α -bromo- β -dimethylacrylate, b. p. 76°/9 mm., n_D^{20} 1.4909 (Found: C, 37.8; H, 4.8. $C_6H_8O_2Br$ requires C, 37.3; H, 4.7%), prepared by esterification of the bromo-acid with methanol and sulphuric acid, since both specimens with aqueous ammonia (d 0.880) gave α -bromo- β -dimethylacrylamide, needles from light petroleum (b. p. 60–80°), m. p. and mixed m. p. 129° (Found: C, 34.0; H, 4.7; N, 7.5. C_6H_8ONBr requires C, 33.7; H, 4.5; N, 7.9%).

Reactions of Methyl α -Bromo- α -olefinic Esters with Methyl Diazoacetate.—(i) A solution of methyl α -bromoacrylate (1 g.) and methyl diazoacetate (2 g.) in light petroleum (b. p. 80–100°) (50 c.c.) was refluxed for 15 hours (during which the intensity of the deep yellow colour was much reduced) and then evaporated to dryness under reduced pressure. The solid residue of methyl pyrazole-3:5-dicarboxylate (1.3 g.) crystallised from water in colourless prisms, m. p. 152° (Found: N, 15.3. Calc. for $C_7H_8O_4N_2$: N, 15.2%). The same product (0.6 g.), m. p. 152°, was also obtained from methyl α -chloroacrylate (1 g.).

(ii) A solution of methyl α -bromocrotonate (1 g.) and methyl diazoacetate (1 g.) in light petroleum (b. p. 80–100°) (25 c.c.) after refluxing for 24 hours was still deeply coloured, in spite of the use of the excess of bromo-ester. Evaporation under reduced pressure gave a small residue of methyl 4-methylpyrazole-3:5-dicarboxylate, colourless prisms (0.15 g.) from water, m. p. 128–129° (Found: C, 48.85; H, 5.2; N, 14.0. $C_8H_{10}O_4N_2$ requires C, 48.5; H, 5.1; N, 14.1%), which was also obtained, in similar yield, from methyl α -chlorocrotonate under the same conditions.

(iii) A solution of methyl α -bromo- β -dimethylacrylate (1 g.) and methyl diazoacetate (1 g.) in light petroleum (b. p. 80–100°) (20 c.c.) was refluxed for 4 days, after which the solvent and diazo-ester were removed under reduced pressure. The residual nitrogen-free liquid, b. p. 70°/6 mm., was unchanged bromo-ester, identified by conversion into the amide, m. p. and mixed m. p. 128°.

Action of Diazomethane on Methyl α -Methoxyacrylate.—The methoxy-ester (1 g.) was treated with

excess of ethereal diazomethane at 20° for 4 days. Removal of solvent gave a liquid, b. p. ca. 135°, which by treatment with aqueous ammonia (*d* 0.880) was converted into 1-methoxycyclopropane-1-carboxamide; this crystallised from light petroleum (b. p. 40–60°) in colourless needles, m. p. 117°, which showed no unsaturation towards alkaline permanganate (Found: C, 52.2; H, 8.0; N, 11.9. $C_5H_9O_2N$ requires C, 52.2; H, 7.9; N, 12.2%).

Action of Methanolic Hydrogen Chloride on Methyl Methoxyacrylate.—The methoxy-ester (1 g.) was dissolved in methanol (5 c.c.) and saturated with dry hydrogen chloride at 0°. After $\frac{1}{2}$ hour, the hydrogen chloride was removed by aeration and finally by neutralisation with barium carbonate. Evaporation of the solvent and extraction of the residue with ether gave methyl α -dimethoxypropionate, b. p. 67°/20 mm., which on treatment with methanolic 2:4-dinitrophenylhydrazine sulphate gave the 2:4-dinitrophenylhydrazone of methyl pyruvate, m. p. 186–187°; it was also characterised by conversion, with aqueous ammonia, into α -dimethoxypropionamide, m. p. 117° (Found: N, 10.5. Calc. for $C_5H_{11}O_3N$: N, 10.5%).

The authors thank Dr. E. A. Braude for the determinations of absorption spectra.

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[Received, November 20th, 1946.]

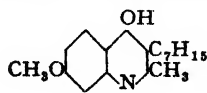
192. Tetrahydroacridones and Related Compounds as Antimalarials.

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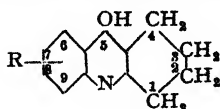
Tetrahydroacridones, 12-hydroxydihydro- β -quinindenes, and 2- and 4-hydroxyquinolines have been examined for antimalarial activity. Marked prophylactic action has been found against *P. gallinaceum* infections in chicks and the structural requirements for activity are outlined. The experimental conditions for the Conrad-Limpach ring-closure of β -arylaminod $\Delta^2\beta$ -unsaturated esters are discussed.

THERE are two approaches to the chemotherapy of malaria. The prophylactic approach aims at rendering the bite of the mosquito ineffective in producing an infection and the therapeutic approach aims at the eradication of an established infection; the former is directed at the sporozoites injected by the mosquito and the subsequent (primary) tissue phase development, while the latter aims at control during the later erythrocytic stages in the developmental cycle of the parasite. Quinine, mepacrine, and pamaquin, to which paludrine and several 4-dialkylaminoalkylaminoquinolines may now be added, are well-established examples of drugs possessing the latter type of action but, until recently, there have been few reports of drugs exhibiting causal prophylactic activity. Pamaquin has a slight prophylactic action (Kikuth and Mudrow, *Z. Immun-Forsch.*, 1939, 95, 285; Mudrow, *Arch. Schiffs- u. Tropen-Hygiene*, 1940, 44, 257). Certain sulphonamides (Sinton, Hutton, and Shute, *Ann. Trop. Med. Parasit.*, 1939, 33, 37; Coatney and Cooper, *Publ. Hlth. Rep., Wash.*, 1944, 59, 1455; Coggeshall, Porter, and Laird, *Proc. Soc. Exp. Biol. Med.*, 1944, 57, 286; Freire and Paraense, *Rev. Brasil. Biol.*, 1944, 4, 27) have a marked causal prophylactic action, as does paludrine (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, 39, 208), while *p*-methylsulphonylbenzamidine (Fuller, Tonkin, and Walker, *J.*, 1945, 633) and some arylguanidines (King and Tonkin, *J.*, 1946, 1063) have a slight effect. When the war in Europe ended, reports came to hand (Fitch, *Pharm. J.*, 1945, 155, 182; *Combined Intelligence Objectives Sub-Committee*, 1945, Item No. 24, File No. XXIII-12; *idem*, File No. XXIV-20; *idem*, File No. XXV-54) that German workers had encountered causal prophylactic activity in certain 4-hydroxyquinolines, notably 4-hydroxy-7-methoxy-3-*n*-heptylquinaldine (I) (endochin), and the present authors at once recorded, in a preliminary way, similar observations with a chemically related series (*Nature*, 1945, 156, 629); the present paper describes this work in detail.

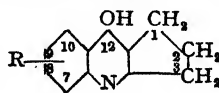
An examination of a number of tetrahydroacridones (II), 12-hydroxy-2:3-dihydro- β -quinindenes (III) (for numbering, see Blount, Perkin, and Plant, *J.*, 1929, 1976), and 2- and 4-hydroxyquinolines for causal prophylactic activity in *Plasmodium gallinaceum* infections in chicks revealed definite activity in compounds conforming to type (IV), of which (I), (II), and



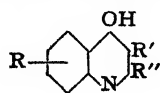
(I.)



(II.)



(III.)



(IV.)

(III) are representative, R' and R'' being saturated hydrocarbon residues. For example, 3-methoxyacridone showed no activity while its tetrahydro-derivative, 7-methoxy-1:2:3:4-

tetrahydroacridone (V), was the most active substance encountered, being, on a weight basis, about twice as active as sulphadiazine and four times as active as endochin (I), our investigations being ultimately extended to include comparison with this substance. Access to compounds of types (II), (III), and (IV) was obtained by condensation of the appropriate aromatic primary amines and β -keto-esters, followed by thermal cyclization of the resulting β -arylamino- $\Delta^{\alpha\beta}$ -unsaturated esters. This reaction was described first for ethyl acetoacetate by Conrad and Limpach (*Ber.*, 1887, 20, 944) who simply heated the intermediate products to about 250° and rarely obtained yields greater than 30%. The reaction was used by numerous workers in the interval and many years elapsed before Limpach (*Ber.*, 1931, 64, 969; D.R.-P. 455,387) made the significant improvement of effecting ring-closure by adding the intermediate products to liquid paraffin preheated to 250—280° and claimed yields of over 90%. Our own experience has been that decomposition is frequently excessive under Limpach's conditions as the products separate on the walls of the reaction vessel and there become overheated, and the yields are not as good as those claimed; other criticisms have been advanced by Maurin (*Ann. Chim.*, 1935, 4, 309). Ashley *et al.* (*Proc. Roy. Soc.*, 1933, B, 113, 295) used molten paraffin wax which was subsequently removed by a solvent. It was obvious to us that the best thermal control and mixing could be obtained by using a vigorously boiling inert solvent of suitable boiling point. For several years, therefore, we have used vigorously boiling diphenyl (b. p. 255°) for this purpose and have obtained clean products in good yield thereby; American workers (Price and Roberts, *J. Amer. Chem. Soc.*, 1946, 68, 1204; Steck, Hallock, and Holland, *ibid.*, p. 1241) have recently described the use of diphenyl ether and the eutectic of diphenyl and diphenyl ether (Dowtherm A) for this purpose, the latter having the advantage of being liquid at room temperature. Other high boiling inert solvents should be equally suitable, quinoline, for example, having been applied for this purpose (Dr. F. H. S. Curd, private communication).

With *o*- and *p*-substituted amines the constitutions of the products formed in the Conrad-Limpach reaction are unequivocal. With *m*-substituted amines, however, two products may be obtained since ring-closure may take place at either the 2- or the 6-position of the arylamino-group; both were isolated in the ring-closures of ethyl 2-*m*-anisidinocyclohex-1-enecarboxylate, which yielded 8- (VI) and 6-methoxy-1 : 2 : 3 : 4-tetrahydroacridone (VII), and ethyl β -*m*-anisidino- α -*n*-heptylcrotonate, which yielded endochin (I), m. p. 213—214°, and the isomeric 4-hydroxy-5-methoxy-3-*n*-heptylquinaldine (VIII), m. p. 219—220°. Leonard, Herbrandson, and Van Heyningen (*J. Amer. Chem. Soc.*, 1946, 68, 1279) have recently studied the latter ring-closure but do not record the isolation of (VIII) and claim, on the basis of analytical data, to have isolated the demethylated substance, 4 : 5-dihydroxy-3-*n*-heptylquinaldine, m. p. 218—218.5° (corr.), in addition to (I), m. p. 218.5—219.5° (corr.). In both these cases ring-closure at the position para to the methoxyl group greatly preponderated, in contrast with the purely aromatic series where approximately equal proportions of 2- and 4-methoxyacridones are formed in the ring-closure of *N*-*m*-anisylantranilic acid (Lehmstedt and Schrader, *Ber.*, 1937, 70, 838). An authentic specimen of (VI) was obtained by applying the Niementowski-Borsche-Tiedtke reaction to 4-methoxyanthranilic acid and cyclohexanone, but the yield was poor because of the ease with which this particular anthranilic acid undergoes decarboxylation. The melting points of 7-methoxy- (V) and 7-ethoxy-1 : 2 : 3 : 4-tetrahydroacridone (X) recorded here differ from those recorded in the literature (see pp. 1036, 1037), but we have carefully repeated these preparations and have fully confirmed our own observations.

Tests for causal prophylactic activity in *P. gallinaceum* infections in 10-day old chicks were carried out using the technique previously outlined (Fuller, Tonkin, and Walker, *loc. cit.*; King and Tonkin, *loc. cit.*) and the results are recorded in the Table. The minimal effective doses are those, given orally twice daily for the first four days and commencing two hours before infection, which gave definite indications of activity in comparison with untreated controls. In some cases no parasites were observed in the blood during the period of observation; sub-inoculations into clean chicks from such birds were carried out in a few cases and, if no infection resulted in the recipients, the donors were considered as having been sterilized of their infections (S). Where no sub-inoculations were carried out the result is recorded as presumably sterilized (? S). These observations (S and ? S) were, of course, made on higher dosages than those recorded as minimal. In a number of cases tests for therapeutic activity were carried out and the results are recorded in the Table; + denotes definite action, +— slight action, and — no action. The following substances, prepared by known methods, were also examined for prophylactic action and found to be inactive: 2 : 4-dihydroxyquinoline, 4-hydroxyquinaldine, 4-hydroxy-6-methoxyquinaldine, 4-hydroxy-8-methoxyquinaldine, 2-hydroxy-6-methoxy-lepidine, 1 : 2 : 3 : 4-tetrahydroacridone, and 3-methoxyacridone. From an inspection of the

Table and the preceding list, it is obvious that activity was only to be found in substances conforming to type (IV), as mentioned above. The necessity for the presence of a substituent in the benzene ring is clearly indicated by the inactivity of the simple 1:2:3:4-tetrahydroacridone and, of the substituents examined, methoxyl was more favourable than chloro-, which was more favourable than the ethoxyl group as indicated by the order of activities, (V) > (XI) > (X), and (XXIV) = (XXVI) > (XXV). The effect of the position of the methoxyl group in the benzene ring was marked, the position corresponding to the 7-position of quinoline being as a rule favourable as indicated by endochin (I), in which R' and R'' of (IV) are of unequal size, but where R' and R'' are of equal size as in (V), (VI), and (IX) the position corresponding to the 6-position of quinoline appeared to be most favourable, and weighting the alicyclic ring had a dystherapeutic effect.

EXPERIMENTAL.

General Method for the Synthesis of 1:2:3:4-Tetrahydroacridones, 12-Hydroxy-2:3-dihydro- β -quinindenes, and 4-Hydroxyquinolines.—Equimolecular amounts, usually 0.1 g.-mol., of the appropriate aromatic primary amine and β -keto-ester were mixed—with warming, if necessary, in the case of solid amines—and the mixture, treated with one drop of concentrated hydrochloric acid (Coffey, Thomson, and Wilson, *J.*, 1936, 856), was set aside in a partly evacuated desiccator for several days at 37°. The crude β -arylamino- Δ^{β} -unsaturated esters were cyclized by being added slowly to a weight of boiling diphenyl four times that of the combined starting materials. Evolution of alcohol took place readily and the boiling solutions were refluxed for 15 minutes after the end of the addition. On cooling, the products usually crystallised when the temperature fell to about 100°. When cold, the diphenyl was removed with ether, and the crude products, usually cream-coloured, were crystallised from suitable

Antimalarial Activity in P. gallinaceum Infections.

Tetrahydroacridones:	Prophylactic Test.		Therapeutic Test.
	Min. effective dose (mg./100 g. chick).	Remarks.	
(V) 7-Methoxy-.....	12.5	?S	+
(VI) 8-Methoxy-.....	25		+—
(IX) 9-Methoxy-.....	37.5		—
(X) 7-Ethoxy-.....	inactive		
(XI) 7-Chloro-.....	100	slight act.	—
(XII) 7-Methyl-.....	inactive *		
(XIII) 7:8-Dimethoxy-.....	inactive *		
(XIV) 7-Methoxy-3-methyl-.....	inactive *		
(XV) 8-Methoxy-3-methyl-.....	50	S	
(XVI) 9-Methoxy-3-methyl-.....	50		
(XVII) 7-Methoxy-1-methyl-.....	62.5	toxic	
(XVIII) 8-Methoxy-1-methyl-.....	ca. 25	S	
(XIX) 9-Methoxy-1-methyl-.....	50	toxic	
(XX) 7-Methoxy-3-ethyl-.....	inactive *		
(XXI) 8-Methoxy-3-ethyl-.....	100	?S	
(XXII) 9-Methoxy-3-ethyl-.....	inactive *		
(XXIII) 7-Methoxy-1-ethyl-.....	100	very slight	
Dihydro- β -quinindenes:			
(XXIV) 12-Hydroxy-9-methoxy-.....	37.5		+
(XXV) 12-Hydroxy-9-ethoxy-.....	inactive		
(XXVI) 12-Hydroxy-9-chloro-.....	31		+
4-Hydroxyquinolindines:			
(XXVII) 6-Methoxy-3-ethyl-.....	inactive	toxic	
(XXVIII) 6-Methoxy-3-n-heptyl-.....	inactive *		
(I) 7-Methoxy-3-n-heptyl-.....	50	S	+
(XXIX) 8-Methoxy-3-n-heptyl-.....	ca. 100		
Sulphadiazine	25		

* Highest dose tested: 100 mg.

solvents. Diphenyl was used in the same arbitrarily selected proportion throughout, but recent work (Price and Roberts, *loc. cit.*) indicates that there may be an optimal concentration for each particular ring-closure.

7-Methoxy-1:2:3:4-tetrahydroacridone (V).—Obtained in an overall yield of 86% from *p*-anisidine and ethyl cyclohexanone-2-carboxylate, the compound crystallised from alcohol or, better, pyridine in flat rectangular plates, m. p. 313° (Found: C, 73.6; H, 6.6; N, 6.3. Calc. for $C_{14}H_{15}O_2N$: C, 73.4; H, 6.6; N, 6.1%). Basu and Das Gupta (*J. Indian Chem. Soc.*, 1937, 14, 468) record m. p. 295°; Hughes and Lions (*J. Proc. Roy. Soc., New South Wales*, 1938, 71, 458) record m. p. 284°; Bukhsh and Desai (*Proc. Indian Acad. Sci.*, 1939, A, 10, 262) record m. p. 285–286°. The intermediate ethyl 2-*p*-anisidino-cyclohex-1-enecarboxylate separated from methyl alcohol in prisms, m. p. 70° (Found: C, 66.7; H, 7.7;

N, 5.4. Calc. for $C_{14}H_{15}O_2N$: C, 69.9; H, 7.6; N, 5.1%. Hughes and Lions (*loc. cit.*) record m. p. 71°; Bukhsh and Desai (*loc. cit.*) record m. p. 71–72°.

8-Methoxy-1 : 2 : 3 : 4-tetrahydroacridone (VI).—(a) 4-Methoxyanthranilic acid (4 g.) (preparation below) and cyclohexanone (4 g.) were mixed and heated to 220° fairly rapidly and the mixture was kept at 220–230° for an hour. The mixture was cooled and treated with ether to remove *m*-anisidine, arising from decarboxylation, and unreacted cyclohexanone. The insoluble 8-methoxytetrahydroacridone (0.3 g.; 5%) separated from spirit in small hexagonal plates, m. p. 309° (Found: C, 73.0; H, 6.5; N, 6.3. $C_{14}H_{15}O_2N$ requires C, 73.4; H, 6.6; N, 6.1%). The *m*-anisidine, arising as a by-product, was characterised as the acetyl derivative, m. p. and mixed m. p. 80°.

(b) The crude cyclization product obtained in 72% yield from *m*-anisidine and ethyl cyclohexanone-2-carboxylate was a mixture of the 8- and 6-methoxy-compounds which could not be separated satisfactorily by crystallisation. The mixture (17 g.) was therefore dissolved in twice its weight of warm glacial acetic acid and then treated with 1½ volumes of concentrated hydrochloric acid. The hydrochloride, which separated on cooling in the ice-chest, was collected and drained thoroughly. The base (10.7 g.), regenerated from the solid hydrochloride with aqueous ammonia, then separated from spirit in hexagonal plates, m. p. and mixed m. p. 309° (Found: C, 73.1; H, 6.5; N, 6.3%).

6-Methoxy-1 : 2 : 3 : 4-tetrahydroacridone (VII).—The acetic-hydrochloric acid mother liquors from the above experiment, on evaporation to dryness and treatment with aqueous ammonia, afforded the crude 6-methoxy-isomer (5.9 g.) which separated from spirit in flattened needles (1.4 g.), m. p. 326°, depressed to 284° on admixture with the 8-methoxy-compound formed in the same reaction (Found: C, 73.5; H, 6.5; N, 6.1. $C_{14}H_{15}O_2N$ requires C, 73.4; H, 6.6; N, 6.1%).

9-Methoxy-1 : 2 : 3 : 4-tetrahydroacridone (IX).—Obtained in 60% yield from *o*-anisidine and ethyl cyclohexanone-2-carboxylate, the compound separated from *n*-butyl alcohol in plates, m. p. 286–288° (Found: C, 73.5; H, 6.6; N, 6.4. Calc. for $C_{14}H_{15}O_2N$: C, 73.4; H, 6.6; N, 6.1%). Hughes and Lions (*loc. cit.*) record m. p. 278°; Bukhsh and Desai (*loc. cit.*) record m. p. 277–279°.

7-Ethoxy-1 : 2 : 3 : 4-tetrahydroacridone (X).—Obtained in 87% yield from *p*-phenetidine and ethyl cyclohexanone-2-carboxylate, the compound separated from pyridine in needles or from alcohol in prisms, m. p. 292–293° (Found: C, 74.1; H, 7.1; N, 5.8. Calc. for $C_{15}H_{17}O_2N$: C, 74.1; H, 7.0; N, 5.8%). Hughes and Lions (*loc. cit.*) record m. p. > 300°; Bukhsh and Desai (*loc. cit.*) record m. p. > 350°. The intermediate ethyl 2-*p*-phenetidino-cyclohex-1-enecarboxylate separated from alcohol in long prisms, m. p. 87° (Found: C, 70.0; H, 8.0; N, 4.9. Calc. for $C_{17}H_{23}O_3N$: C, 70.6; H, 8.0; N, 4.9%). Hughes and Lions (*loc. cit.*) record m. p. 87°; Bukhsh and Desai (*loc. cit.*) record m. p. 88°.

7-Chloro-1 : 2 : 3 : 4-tetrahydroacridone (XI).—Obtained in 74% yield from *p*-chloroaniline and ethyl cyclohexanone-2-carboxylate, the compound crystallised from alcohol in microscopic prisms, m. p. > 330° (Found: C, 67.0; H, 5.3; N, 6.2. Calc. for $C_{13}H_{12}ONCl$: C, 66.9; H, 5.1; N, 6.0%). Basu and Das Gupta (*loc. cit.*) record m. p. 380°. The intermediate ethyl 2-*p*-chloroanilino-cyclohex-1-enecarboxylate separated from aqueous alcohol in short prisms, m. p. 67°, whereas Basu and Das Gupta (*loc. cit.*) record m. p. 90° (Found: C, 64.7; H, 6.7; N, 5.2. Calc. for $C_{15}H_{18}O_2NCl$: C, 64.4; H, 6.4; N, 5.0%).

7-Methyl-1 : 2 : 3 : 4-tetrahydroacridone (XII).—Obtained in 40% yield from *p*-toluidine and ethyl cyclohexanone-2-carboxylate, the compound separated from aqueous acetic acid in thin laths, m. p. > 330° (Found: C, 78.9; H, 7.1; N, 6.8. Calc. for $C_{14}H_{15}ON$: C, 78.9; H, 7.0; N, 6.6%). Sen and Basu (*J. Indian Chem. Soc.*, 1930, 7, 435) record m. p. 340°; Reed (*J.*, 1944, 425) records m. p. 374°.

7 : 8-Dimethoxy-1 : 2 : 3 : 4-tetrahydroacridone (XIII).—Obtained in 65% yield from 4-aminoveratrole and ethyl cyclohexanone-2-carboxylate, the compound separated from aqueous alcohol in microscopic plates, m. p. > 330° (Found: C, 69.9; H, 6.6; N, 5.6. Calc. for $C_{15}H_{17}O_3N$: C, 69.5; H, 6.6; N, 5.4%). Lions (*ibid.*, p. 242) records m. p. > 300°.

12-Hydroxy-9-methoxy-2 : 3-dihydro- β -quinindene (XXIV).—Obtained in 59% yield from *p*-anisidine and ethyl cyclopentanone-2-carboxylate, the compound separated from alcohol in fine needles, m. p. > 330° with prior darkening (Found: C, 72.7; H, 6.3; N, 6.7. $C_{13}H_{13}O_2N$ requires C, 72.6; H, 6.1; N, 6.5%). The intermediate ethyl 2-*p*-anisidinocyclopent-1-enecarboxylate separated from aqueous alcohol in short needles, m. p. 54–55° (Found: C, 69.0; H, 7.3. $C_{15}H_{19}O_3N$ requires C, 68.9; H, 7.3%).

12-Hydroxy-9-ethoxy-2 : 3-dihydro- β -quinindene (XXV).—Obtained in 59% yield from *p*-phenetidine and ethyl cyclopentanone-2-carboxylate, the compound crystallised from alcohol in aggregates of irregular plates, m. p. approx. 300° with previous darkening (Found: C, 73.4; H, 6.1; N, 6.2. $C_{14}H_{15}O_2N$ requires C, 73.4; H, 6.6; N, 6.1%). The intermediate ethyl 2-*p*-phenetidino-cyclopent-1-enecarboxylate separated from spirit in short prisms, m. p. 53° (Found: C, 70.0; H, 7.7; N, 5.1. $C_{16}H_{21}O_3N$ requires C, 69.9; H, 7.6; N, 5.1%).

9-Chloro-12-hydroxy-2 : 3-dihydro- β -quinindene (XXVI).—Obtained in 60% yield from *p*-chloroaniline and ethyl cyclopentanone-2-carboxylate, the compound crystallised from aqueous acetic acid in long needles, m. p. approx. 330° with prior darkening (Found: C, 65.8; H, 4.5; N, 6.6. $C_{12}H_{10}ONCl$ requires C, 65.8; H, 4.6; N, 6.4%).

7-Methoxy-3-methyl-1 : 2 : 3 : 4-tetrahydroacridone (XIV).—Obtained in 40% yield from *p*-anisidine and ethyl 4-methylcyclohexanone-2-carboxylate, the compound separated from 50% alcohol or aqueous pyridine in microscopic rectangular plates, m. p. 346–347° (Found: C, 73.9; H, 7.1; N, 6.1. Calc. for $C_{15}H_{17}O_2N$: C, 74.1; H, 7.0; N, 5.8%). Basu and Das Gupta (*loc. cit.*) record m. p. 335°.

8-Methoxy-3-methyl-1 : 2 : 3 : 4-tetrahydroacridone (XV).—Presumably contaminated initially with the 6-methoxy-isomer in the reaction product obtained in 56% yield from *m*-anisidine and ethyl 4-methylcyclohexanone-2-carboxylate, the compound separated from pyridine in microscopic needles, m. p. 324° (Found: C, 74.2; H, 6.8; N, 6.1. $C_{15}H_{17}O_2N$ requires C, 74.1; H, 7.0; N, 5.8%).

9-Methoxy-3-methyl-1 : 2 : 3 : 4-tetrahydroacridone (XVI).—Obtained in 62% yield from *o*-anisidine and ethyl 4-methylcyclohexanone-2-carboxylate, the compound separated from alcohol in rectangular plates, m. p. 270–273° (Found: C, 73.7; H, 7.1; N, 6.1. $C_{15}H_{17}O_2N$ requires C, 74.1; H, 7.0; N, 5.8%).

7-Methoxy-1-methyl-1 : 2 : 3 : 4-tetrahydroacridone (XVII).—Obtained in 41% yield from *p*-anisidine and ethyl 6-methylcyclohexanone-2-carboxylate, the compound separated from aqueous alcohol in

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rectangular plates, m. p. 280—281° (Found: C, 73.8; H, 7.0; N, 5.7. $C_{18}H_{19}O_2N$ requires C, 74.1; H, 7.0; N, 5.8%).

8-Methoxy-1-methyl-1:2:3:4-tetrahydroacridone (XVIII).—Obtained in 23% yield from *m*-anisidine and ethyl 6-methylcyclohexanone-2-carboxylate, the compound crystallised from spirit in fine needles, m. p. 277—278° (Found: C, 74.0; H, 7.2; N, 5.6. $C_{18}H_{19}O_2N$ requires C, 74.1; H, 7.0; N, 5.8%).

9-Methoxy-1-methyl-1:2:3:4-tetrahydroacridone (XIX).—Obtained in 24% yield from *o*-anisidine and ethyl 6-methylcyclohexanone-2-carboxylate, the compound separated from ethyl acetate in small cubes, m. p. 245—246° (Found: C, 74.0; H, 7.4; N, 5.9. $C_{18}H_{19}O_2N$ requires C, 74.1; H, 7.0; N, 5.8%).

7-Methoxy-3-ethyl-1:2:3:4-tetrahydroacridone (XX).—Obtained in 72% yield from *p*-anisidine and ethyl 4-ethylcyclohexanone-2-carboxylate, the compound separated from alcohol in rectangular plates, m. p. 334° (Found: C, 74.9; H, 7.1; N, 5.7. $C_{18}H_{19}O_2N$ requires C, 74.7; H, 7.4; N, 5.4%).

8-Methoxy-3-ethyl-1:2:3:4-tetrahydroacridone (XXI).—Obtained in 64% yield from *m*-anisidine and ethyl 4-ethylcyclohexanone-2-carboxylate, the compound was purified with some difficulty from the 6-methoxy-isomer, formed simultaneously, by crystallisation from methyl alcohol and separated in fine flattened needles, m. p. 291° (Found: C, 74.8; H, 7.4; N, 5.6. $C_{18}H_{19}O_2N$ requires C, 74.7; H, 7.4; N, 5.4%). A pure specimen of the 6-methoxy-isomer was not isolated.

9-Methoxy-3-ethyl-1:2:3:4-tetrahydroacridone (XXII).—Obtained in 64% yield from *o*-anisidine and ethyl 4-ethylcyclohexanone-2-carboxylate, the compound separated from spirit in microscopic prisms, m. p. 218—219° (Found: C, 74.6; H, 7.2; N, 5.6. $C_{18}H_{19}O_2N$ requires C, 74.7; H, 7.4; N, 5.4%). The intermediate ethyl 2-*o*-anisidino-5-ethylcyclohex-1-enecarboxylate separated from methyl alcohol in rectangular plates, m. p. 60° (Found: C, 70.8; H, 8.5; N, 4.9. $C_{18}H_{21}O_2N$ requires C, 71.3; H, 8.3; N, 4.6%).

7-Methoxy-1-ethyl-1:2:3:4-tetrahydroacridone (XXIII).—Obtained in 40% yield from *p*-anisidine and ethyl 6-ethylcyclohexanone-2-carboxylate, the compound separated from methyl alcohol in rectangular plates, m. p. 252—253° (Found: C, 74.9; H, 7.7; N, 5.8. $C_{18}H_{19}O_2N$ requires C, 74.7; H, 7.4; N, 5.4%).

4-Hydroxy-6-methoxy-3-ethylquinaldine (XXVII).—Obtained in 46% yield from *p*-anisidine and ethyl α -heptylacetate, the compound separated from pyridine in fine needles, m. p. 290° (Found: C, 72.0; H, 7.0; N, 6.6. $C_{18}H_{21}O_2N$ requires C, 72.0; H, 7.0; N, 6.5%).

4-Hydroxy-6-methoxy-3-*n*-heptylquinaldine (XXVIII).—Obtained in 77% yield from *p*-anisidine and ethyl α -*n*-heptylacetate, the compound separated from methyl alcohol in fine rectangular plates, m. p. 236—237° (Found: C, 75.6; H, 8.9; N, 5.0. $C_{18}H_{25}O_2N$ requires C, 75.3; H, 8.7; N, 4.9%).

4-Hydroxy-7-methoxy-3-*n*-heptylquinaldine (*Endochin*) (I) and 4-Hydroxy-5-methoxy-3-*n*-heptylquinaldine (VIII).—A mixture of isomers was obtained in 61% yield from *m*-anisidine and ethyl α -*n*-heptylacetate, which were allowed to interact in the first stage for 7 days at 37°. Crystallisation from methyl alcohol readily afforded the bulk (*ca.* 2/3) of the product, consisting of (I), which separated in fine flattened needles, m. p. 213—214° (Found: C, 75.7; H, 8.5; N, 5.2. Calc. for $C_{18}H_{25}O_2N$: C, 75.3; H, 8.7; N, 4.9%). Combined Intelligence Objectives Sub-Committee, 1945, Item No. 24, File No. XXV—54 (p. 38) records m. p. 207—212°; Leonard *et al.* (*loc. cit.*) record m. p. 218.5—219.5° (*corr.*).

The mother liquors on concentration to small bulk afforded an obvious mixture (7.9 g.), m. p. 180—185°. This mixture on treatment with *n*-hydrochloric acid (100 c.c.) gave a sticky gum which slowly hardened. The solid was collected and the acid filtrate yielded only traces of material (< 0.1 g.) on treatment with excess of ammonia. The solid dissolved readily in methyl alcohol and the clear solution was evaporated to a syrupy consistency. On addition of water (*ca.* 40 c.c.) a sticky gum reappeared, giving way, on addition of methyl alcohol (*ca.* 20 c.c.), to fine needles. These were collected, the mother liquors being retained (see below), and, on treatment in methyl alcoholic solution with aqueous ammonia, afforded a further amount (4.4 g.) of (I), m. p. and mixed m. p. 213—214°. The aqueous methyl alcohol mother liquors, on treatment with aqueous ammonia, afforded (VIII) (2.95 g.), m. p. 213°, depressed to 173—193° on admixture with (I). The pure compound separated from a small volume of methyl alcohol, or from a larger volume of 50% ethyl alcohol, in clusters of fine needles, m. p. 219—220° (Found: C, 75.4; H, 8.5; N, 4.7; OMe, 10.2. $C_{18}H_{25}O_2N$ requires C, 75.3; H, 8.7; N, 4.9; OMe, 10.8%).

4-Hydroxy-8-methoxy-3-*n*-heptylquinaldine (XXIX).—Obtained in 60% yield from *o*-anisidine and ethyl α -*n*-heptylacetate, the compound crystallised from methyl alcohol in fine prisms, m. p. 155—156° (Found: C, 75.1; H, 8.9; N, 5.1. $C_{18}H_{25}O_2N$ requires C, 75.3; H, 8.7; N, 4.9%).

2-Nitro-4-methoxyphenyl Cyanide.—3-Nitro-4-aminoanisole was submitted to the Sandmeyer reaction using a technique previously described (Fuller, Tonkin, and Walker, *loc. cit.*), affording a 75% yield of recrystallised material separating from methyl alcohol in small plates, m. p. 139° (Found: N, 15.7. Calc. for $C_8H_8O_3N_2$: N, 15.7%). Cook *et al.* (*J.*, 1945, 861), using cuprous cyanide, obtained a somewhat lower yield (crude) and record m. p. 140°.

2-Nitro-4-methoxybenzoic Acid.—The preceding cyanide (50 g.) was refluxed for 5 hours with a mixture of equal volumes of glacial acetic acid, concentrated sulphuric acid, and water (each 100 c.c.), crystals separating after about 1½ hours. The cooled mixture was treated with about 2 volumes of water and the product was collected and re-precipitated (45 g.) from solution in aqueous ammonia; m. p. 195—196° as recorded by Simonsen and Rau (*J.*, 1917, 111, 235) and by Ashley, Perkin, and Robinson (*J.*, 1930, 393).

4-Methoxyanthranilic Acid.—The preceding nitro-acid (45 g.) was dissolved in a slight excess of 2*N*-ammonia and hydrogenated in the presence of palladised strontium carbonate (5 g.) at 45 atm. The calculated fall in pressure was observed in about 20 minutes and absorption of hydrogen then ceased. The filtered solution was acidified to about pH 4 and the product (35.4 g.) was collected; m. p. 180° (*efferv.*). On account of ready decarboxylation, recrystallisation from *ca.* 40% aqueous acetic acid was wasteful but afforded fine prisms, m. p. 180—181° (*efferv.*). Friedländer, Bruckner, and Deutsch (*Annalen*, 1912, 385, 46) record m. p. 166° (*decomp.*); Ullmann and Dootson (*Ber.*, 1918, 51, 20) record m. p. 172° (*decomp.*).

Ethyl α -*n*-Heptylideneacetoacetate.—A mixture of freshly distilled oenanthal (100 g.) and ethyl

acetoacetate (114 g.) was cooled in a freezing mixture and saturated with dry hydrogen chloride. After 18 hours in the ice-chest the mixture was poured into water and extracted with ether. The extract was washed well with water, dried, and fractionated, affording a colourless oil (158 g.), b. p. 150–152°/14 mm. (Found: C, 69.1; H, 10.0. Calc. for $C_{13}H_{22}O_3$: C, 69.0; H, 9.7%). Knoevenagel (*Ber.*, 1898, **31**, 737) used piperidine as catalyst and recorded b. p. 145°/10 mm.

Ethyl α -n-Heptylacetate.—The preceding unsaturated ester (145 g.) was hydrogenated in ethyl alcohol (400 c.c.) with palladised strontium carbonate (7 g.) at 45 atm. The calculated fall in pressure was observed in about 20 minutes and no further absorption of hydrogen took place. The product, a colourless oil (133 g.), distilled at 144–146°/11 mm. (Found: C, 68.3; H, 10.5. Calc. for $C_{13}H_{24}O_3$: C, 68.4; H, 10.5%). Wojcik and Adkins (*J. Amer. Chem. Soc.*, 1934, **56**, 2424) record b. p. 130–132°/7 mm.

The authors are greatly indebted to Mr. L. V. Sharp for much preparative assistance and to Mrs. A. M. Yates, B.Sc., for assistance in carrying out antimalarial tests.

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[Received, November 7th, 1946.]

193. β -Phellandrene Tetrabromide.

By P. A. BERRY and A. KILLEN MACBETH.

The optically active tetrabromide isolated from the terpene fraction of *E. cneorifolia* oil is derived from *l*- β -phellandrene and is identical with samples prepared from *l*- β -phellandrene derived from Canada-balsam oil. *d*- β -Phellandrene from water-fennel oil also forms an optically active tetrabromide. The β -phellandrene tetrabromides are characterised by rotations of opposite sign to that of the hydrocarbon from which they are derived.

In a previous paper (Berry, Macbeth, and Swanson, *J.*, 1937, 1443) it was shown that a seasonal variation occurred in the oil of *Eucalyptus cneorifolia* with an increase in the terpene content from a minimum of some 10% to a maximum approaching 50% which is attained during the period of active growth in the early summer months. The presence of *l*- α - and *l*- β -phellandrene was established, and after further examination of the terpene fraction it was reported by Berry and Macbeth (*Nature*, 1945, **156**, 175) that a crystalline tetrabromide can be isolated after bromine vapour has been aspirated through solutions of such terpene fractions in acetic acid, and the reaction mixture stored for some days in the refrigerator. The crystalline tetrabromide is separated in amounts corresponding with upwards of 20% of the total terpene when the hydrocarbon is dissolved in about four times its weight of acetic acid, and excess of bromine introduced whilst the temperature is kept below 0°.

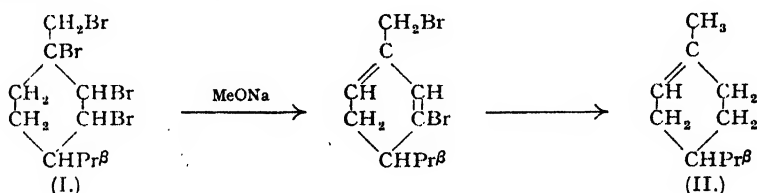
Analysis of the tetrabromide showed the formula to be $C_{10}H_{16}Br_4$, and in view of the fact that the substituent groups in the cyclic compounds occurring in *E. cneorifolia* oil are in the para-positions it may reasonably be concluded that the progenitor of the tetrabromide is a *p*-menthadiene. Of the fourteen possible structures seven inactive compounds are excluded as the tetrabromide is dextrorotatory, and of the remaining seven only two (limonene and *p*-mentha-2 : 8(9)-diene) are optically active and without conjugated double bonds. Henry and Paget (*J.*, 1925, **127**, 1649) isolated from oil of chenopodium an inactive tetrabromide which they considered was derived from *p*-mentha-2 : 8(9)-diene. We have confirmed this observation excepting that our tetrabromide had slight optical activity. The tetrabromides from limonene and dipentene have also been re-examined, and as their properties differ markedly from those of the tetrabromide from *E. cneorifolia* these substances must also be excluded. One is therefore forced to consider the para-menthadienes containing a conjugated system of double bonds despite the fact that crystalline tetrabromides derived from such substances are not described in the literature.

The tetrabromide now described is debrominated by magnesium in ether and yields a hydrocarbon, $C_{10}H_{16}$, which is readily converted into the tetrabromide again. This hydrocarbon showed the characteristics of *l*- β -phellandrene; in particular it formed a nitrosite the mutarotation of which was similar to that of the nitrosite derived from a sample of *l*- β -phellandrene from Canada-balsam oil. Authentic samples of *l*- β -phellandrene gave tetrabromides identical with that derived from the terpene fractions of *E. cneorifolia* oil, in particular having m. p. 118–119° after recrystallisation from ethyl acetate and a specific rotation of approximately +49° in the same solvent, the value being unchanged even after two months. The specific rotation in chloroform was higher (+53.6°) and these solutions too showed little change in rotation on storage.

The chief feature of the tetrabromide derived from β -phellandrene is the change of sign of

rotation, the levorotatory hydrocarbon giving a dextrorotatory tetrabromide. This characteristic property provides a convenient and useful criterion for β -phellandrene, the identification of which has hitherto mainly rested on the optical properties of derivatives such as the nitrosite. A sample of *d*- β -phellandrene from water-fennel oil was available (Berry, Macbeth, and Swanson, *J.*, 1937, 1448), and this yielded a tetrabromide having m. p. 118–119° which had a specific rotation of the same magnitude as that derived from *l*- β -phellandrene but of opposite sign.

Wallach (*Annalen*, 1894, 281, 129) examined the debromination of limonene tetrabromide by sodium methoxide and obtained as a product a monobromo-compound which nascent hydrogen converted into carveol methyl ether. The reaction with β -phellandrene tetrabromide (I) follows quite a different course, as only two bromine atoms are removed by the methoxide, and nascent hydrogen converts the product into a levorotatory hydrocarbon of low density having the composition $C_{10}H_{18}$. The reactions appear to result in the formation of *l*-*p*-menth-1-ene (II), as the molecular refraction (45.85) agrees with the calculated value (45.7) and the compound forms a nitrosochloride having m. p. 93–94° and $[\alpha]_D -342^\circ$ (ether). The nitrosochloride derived from *d*-*p*-menth-1-ene (Wallach, *Annalen*, 1911, 381, 58; Vavon, *Compt. rend.*, 1911, 152, 1675) has m. p. 95–96° and $[\alpha]_D +344^\circ$, the sign of rotation of the derivative being the same as that of the parent hydrocarbon.



EXPERIMENTAL

Tetrabromide from Terpene Fraction of E. cneorifolia Oil.—Preliminary experiments showed that the amount of tetrabromide formed varied greatly with conditions, and the factors favourable to high yield were mainly (1) the use of freshly distilled terpene fraction dissolved in about four times its volume of acetic acid, (2) a bath temperature below 0° but not so low as to cause much crystallisation of acetic acid on the walls of the reaction vessel, (3) steady aspiration of bromine vapour at such a rate that bromination was completed within an hour and the additional excess of bromine introduced for a further fifteen minutes, (4) efficient stirring to ensure that the temperature of the reaction mixture did not rise above about 5°, and (5) subsequent storage in the refrigerator for several days.

In a typical experiment freshly distilled terpene (100 c.c.) having $\alpha_D -42.4^\circ$ (homogeneous) was dissolved in acetic acid (350 c.c.) and brominated for 70 minutes, the flask being immersed in an ice-salt mixture. Bromine (140 g.) was rapidly absorbed during 45 minutes and aspiration was stopped after an excess (180 g. in all) had been introduced (70 minutes). The mixture was placed in the refrigerator, and crystallisation of the tetrabromide was beginning within an hour. After five days the crystals were removed at the pump and washed with cold acetic acid. Yield, 56 g. of crude tetrabromide having m. p. 109–110°, $[\alpha]_D 57.1^\circ$ in chloroform (*c*, 4.468). This is equivalent to upwards of 20% of the terpene taken.

In another experiment terpene (100 c.c.; $\alpha_D -43.2^\circ$) in acetic acid (400 c.c.) was brominated by aspiration of bromine (195 g.) for an hour, the temperature of the bath being -8° . Some acetic acid crystallised on the walls during reaction and the yield of crude washed tetrabromide collected after seven days was 47 g. having m. p. 109–111, $[\alpha]_D 59.5^\circ$. In a further experiment terpene (75 c.c., $\alpha_D -38^\circ$) in acetic acid (300 c.c.) after treatment in a similar way with bromine (147 g.) gave crude washed tetrabromide (37.3 g.) having m. p. 108–110°, $[\alpha]_D 52.7^\circ$ in chloroform. This corresponds with about 18% of terpene taken.

The combined yields of tetrabromide (140 g.) from the above preparations after four crystallisations from ethyl acetate gave pure tetrabromide as flat glistening plates having m. p. 116–117°, $[\alpha]_D 53.6^\circ$ in chloroform (*c*, 5.41). Further recrystallisation raised the m. p. to 118–119°. The solubility in ethyl acetate at 17° is 10.4% w/w and tetrabromide of good quality can be recovered as a first crop after concentration of the mother liquors. The specific rotation of the tetrabromide in ethyl acetate is somewhat lower than in chloroform, a solution (*c*, 4.004) having a value of 48.8° which was unchanged after the solution had been kept for two months (Found: C, 26.4; H, 3.65; Br, 70.2. $C_{10}H_{18}Br_4$ requires C, 26.3; H, 3.5; Br, 70.1%).

Debromination of the Tetrabromide.—The method of debromination used was essentially that described by Brown and Lemke (*Ber.*, 1923, 56, 1562) in the preparation of limonene from its tetrabromide by the action of magnesium in ether. Purified tetrabromide (39 g.) in anhydrous ether (196 c.c.) was gently warmed with magnesium (6.2 g.) and a trace of iodine. After 90 minutes the ethereal layer was separated and washed with water (twice), and the washings were used to wash the original lower (magnesium bromide) layer. The separated ether from this was washed with water and the total ether distilled to remove solvent and then steam distilled. From two such experiments unchanged tetrabromide (5.3 g.) was recovered from the steam-distillation flask, and an oil (15.8 g.) of low density ($d_{4^\circ} 0.843$) was recovered from the distillate. The hydrocarbon obtained on distilling the oil over sodium had $d_{4^\circ} 0.8411$ and $[\alpha]_D^{20} -16.2^\circ$. It had the formula $C_{10}H_{18}$ and gave a nitrosite (Found: C, 88.3; H, 11.95. Calc.:

C, 88.15; H, 11.8%). When brominated as described above the hydrocarbon gave a tetrabromide identical with the original.

Tetrabromide of *l*- β -Phellandrene.—The formation of a nitrosite suggested that the hydrocarbon was possibly a phellandrene, and this was supported by the fact that a terpene fraction from which the phellandrene was removed gave, on bromination, only a small quantity of crystals which were inactive and had m. p. 220°. This was evidently benzene hexabromide derived from traces of benzene in the solvents used during removal of the phellandrene as nitrosite. The bromination of *l*- β -phellandrene was therefore examined, the material being available as an old sample derived from Canada-balsam oil. On steam distillation this gave terpene having $\alpha_D -42^\circ$, and after bromination as described above crude tetrabromide (7.2 g.) was obtained in amount equivalent to about 10% of the terpene. It had m. p. 110–112°, $[\alpha]_D^{20} 57.3^\circ$ in ethyl acetate (c. 4.265), and after several recrystallisations from the same solvent the m. p. had risen to 116–117°. The sample showed no depression of m. p. on admixture with the pure tetrabromide derived from *E. cneorifolia* oil.

A small sample of the residue from water fennel oil from which *d*-cryptone and *d*-phellandral had been removed some years before was steam distilled, and the terpene collected (which contained *d*- β -phellandrene and was dextrorotatory) was brominated in the usual way. The crude tetrabromide of *d*- β -phellandrene had m. p. 111–113° and a high *l*ævo-rotation ($[\alpha]_D -56.6^\circ$) in ethyl acetate (c. 5.492). After four recrystallisations from ethyl acetate the pure tetrabromide had m. p. 116–116.5°, and $[\alpha]_D^{20} -55.1^\circ$ in ethyl acetate (c. 4.046). The m. p. of the substance is the same as that of the tetrabromide of *l*- β -phellandrene and its optical activity of the same order, but of opposite sign.

The tetrabromide of *dl*- β -phellandrene was separated as long needles when a solution of equimolecular amounts of the *d*- and the *l*-compound in ethyl acetate was allowed to evaporate slowly. The substance was inactive and had m. p. 112–113°, not changed by further crystallisation.

Debromination by Sodium Methoxide.—The tetrabromide of *l*- β -phellandrene (50 g.) was refluxed for more than 8 hours with sodium methoxide (8 g. sodium in 100 c.c. of methyl alcohol). After the addition of some water the reaction mixture was steam distilled, and the oil (30 g.) recovered from the distillate was dried (KOH) and fractionated under reduced pressure. It distilled as a main fraction (28 g.) which was again refluxed for 7 hours with sodium methoxide, and the oil was worked up again giving a main fraction (26 g.) which distilled at 144–148°/11 mm. and had *d* 1.448; $[\alpha]_D 19.2^\circ$; $n_D^{20} 1.5643$. Bromine combined as sodium bromide in the still residue after the steam distillations amounted in the first case to 18.5 g. which is equivalent to the removal of 2.1 atoms of bromine from the tetrabromide. After the second treatment with methoxide bromine removed was assayed as equivalent to a further 0.2 atom only.

The partly debrominated oil (24 g.) was dissolved in absolute alcohol (250 c.c.) and gradually treated with sodium (20 g.), the mixture being heated on the water-bath as reaction slowed down. The oil collected on steam distillation still contained bromine and was again subjected to the action of nascent hydrogen. The oil then collected on steam distillation, after being dried (KOH), distilled at 75–76°/34 mm. and had $d_{15.5}^{20} 0.8228$; $[\alpha]_D -81.2^\circ$ (homogeneous); $n_D^{20} 1.4581$ (Found: C, 87.2; H, 13.0. Calc. for $C_{10}H_{18}$: C, 86.85; H, 13.1%). The oil readily decolorised bromine in acetic acid and gave a nitrosochloride, m. p. 93–94°, which was very stable and did not decompose on heating to 140°. In ether (c. 0.714) the nitrosochloride had $[\alpha]_D -342^\circ$ which had fallen after 13 hours to -322° and after 85 hours to -280° . It appears that the compound is *l*-*p*-menth-1-ene as the constants are in good agreement with those recorded for *d*-*p*-menth-1-ene, the optical values being of opposite sign.

Other Tetrabromides.—In the course of the work several tetrabromides were prepared for comparison with the product obtained from *E. cneorifolia* oil. *d*-Limonene tetrabromide was prepared from sweet orange oil of pharmaceutical quality, and had m. p. 104–105°, $[\alpha]_D 79.2^\circ$ in chloroform. Dipentene tetrabromide was prepared from a sample of dipentene kindly supplied by Professor T. G. Jones, and a further preparation was carried out from cineol. The tetrabromide was inactive and had m. p. 126–127°. A tetrabromide was also prepared from an imported sample of pharmaceutical oil of chenopodium; it had m. p. 115–116°, $[\alpha]_D 2.2^\circ$ in chloroform (c. 16.13) (compare Henry and Paget, *loc. cit.*).

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[Received, October 23rd, 1946.]

194. *Molecular Rearrangement and Displacement of Arylamine Residues in α -Arylamino-ketones. Part I.*

By R. M. COWPER and T. S. STEVENS.

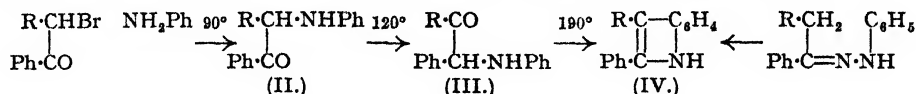
When an arylaminodeoxybenzoin (e.g., II) is heated with a mixture of an arylamine and its hydrobromide, rearrangement may take place (to III); if the arylamine does not correspond to the arylamine residue in the ketone, this residue may be displaced by that of the reagent, with or without simultaneous rearrangement. The observations are only partly explicable by the mechanism proposed by Bischler for the rearrangements and displacements involved in the conversion of phenacylarylamines into arylindoles, and other mechanisms are discussed.

McGEOCH and STEVENS (J., 1935, 1032) observed that the action of aniline on phenyl 1-bromo-2-phenylethyl ketone afforded an anomalous by-product (I):

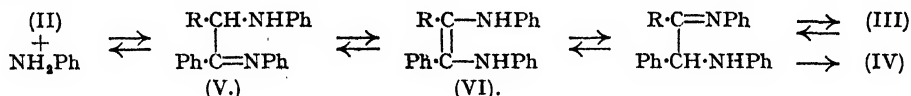


Related reactions of more tractable materials have been studied in detail, and the observations and tentative conclusions are reported now in view of publications by other workers in the same field (Crowther, Mann, and Purdie, *J.*, 1943, 58; Verkade and Janetzky, *Rec. Trav. chim.*, 1943, 62, 763, 775; Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, 67, 1203). The results of the principal series of experiments are summarised in the table.

The α -bromo-derivatives of 4- and 4'-methoxydeoxybenzoin react in the first instance normally, by direct displacement, with aniline, *p*-toluidine, or methylaniline (Cowper and Stevens, *J.*, 1940, 347; which see for proofs of constitution of substances described in this paper); but at higher temperatures, in presence of arylamine and arylamine hydrobromide, such transformations as the following may occur (R = *p*-anisyl, throughout) :



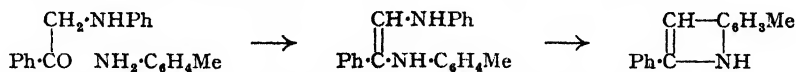
The conversion of the base (II) into (III) is sensibly complete, like the thermal transformation (Julian and Passler, *J. Amer. Chem. Soc.*, 1932, 54, 4756; cf. Luis, *J.*, 1932, 2547) of the corresponding benzoin into its isomeride, $\text{R}\cdot\text{CH}(\text{OH})\cdot\text{COPh} \rightarrow \text{R}\cdot\text{CO}\cdot\text{CH}(\text{OH})\text{Ph}$. It is plausibly explained on the basis of Bischler's mechanism for the formation of 2-phenylindole from anilinoacetophenone (*Ber.*, 1892, 25, 2860; 1893, 26, 1336; cf. Strain, *J. Amer. Chem. Soc.*, 1929, 51, 270) :



This explanation does not exclude rearrangement of the *N*-methyl derivative of (II) in presence of methylaniline and its hydrobromide, through direct formation and hydrolysis of the intermediate (as VI); but the process might be expected to be more difficult, in view of the failure of the carbonyl group of benzoin to react with a secondary base (Cowper and Stevens, *loc. cit.*). In fact, no reaction was observed below 170°, higher temperatures leading, not to the methyl derivative of (III), but by indolisation to that of (IV). Indolisation is structurally excluded in *phenyl α -(N-methylmesidino)-p-methoxybenzyl ketone*, $\text{Ph}\cdot\text{CO}\cdot\text{CHR}\cdot\text{NMe}\cdot\text{C}_6\text{H}_4\text{Me}_3$, but when this was heated with methylmesidine and its hydrobromide at 170° it was recovered unchanged, and at 190° the only isolable product was nitrogen-free.

Julian *et al.* (*loc. cit.*) record similar (reversible) rearrangements, *i.e.*, (II; R = Me or CH_2Ph) \rightarrow (III; R = Me or CH_2Ph), and also demonstrate the formation, under similar experimental conditions, of anilinodeoxybenzoin anil (as V) from anilinodeoxybenzoin and aniline.

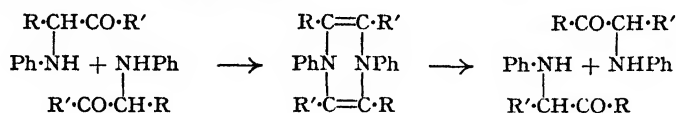
The Bischler mechanism accounts well for the conversion of anilinoacetophenone, by heating with excess of *p*-toluidine and its hydrochloride, into 2-phenyl-5-methylindole, aniline being in effect displaced by toluidine (Bischler, *loc. cit.* For other examples, see Julian *et al.*, *J. Amer. Chem. Soc.*, 1933, 55, 2105; 1945, 67, 1203; Verkade and Janetzky, *loc. cit.*) :



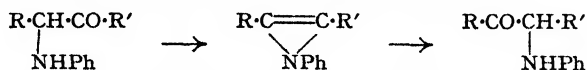
Such a displacement is not necessarily associated with indolisation; thus when (II) or (III) is heated at 120° with excess of *p*-toluidine and *p*-toluidine hydrobromide the product is the toluidino-analogue of (III), displacement being accompanied in the former case by rearrangement. Further similar results are recorded in the table.

The reactions of rearrangement and/or displacement so far discussed can be accommodated by the Bischler-Strain scheme; alternatively, a somewhat similar mechanism could be envisaged, involving as an intermediate stage a product of the type $(\text{NHAr}\cdot\text{CR}\cdot\text{CPh})_2\text{NAr}$, discovered by Crowther, Mann, and Purdie (*loc. cit.*); but it is not clear why the *N*-methyl derivatives of (II) and (III) are unaffected by aniline-aniline hydrobromide up to 170°; and most surprising that (II), with methylaniline and its hydrobromide, readily affords (III) by rearrangement without displacement. The rearrangement of (II) is, moreover, smoothly effected by boiling with pyridine hydrobromide in pyridine or in butyl alcohol, a result explicable on Bischler's hypothesis only if part of the initial material furnishes free aniline by decomposition. This remote possibility was examined, and the strictly intramolecular character of the rearrangement

indicated, by heating a mixture of two arylamino-ketones with pyridine hydrobromide in pyridine and seeking evidence for an exchange of arylamine residues. For experimental convenience, one selected initial substance was desylanthranilic acid, $\text{Ph}\cdot\text{CO}\cdot\text{CHPh}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$, rearrangement of which is concealed by symmetry but from which aniline readily displaces anthranilic acid. The second initial material was (II), and the only products, isolated in good yield, were (III) and desylanthranilic acid. The result also discredits such a mechanism as the following (cf. Gabriel, *Ber.*, 1908, **41**, 1146) :



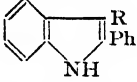
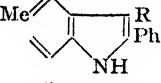
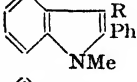
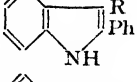
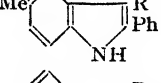
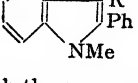
A strictly intramolecular rearrangement can be formulated in conventional structural terms only by postulating an intermediate having a three-membered ring :



For unsaturated C_2N rings compare Neber and Burgard (*Annalen*, 1932, **493**, 281).

Attempts were also made to effect the displacement of one arylamine by another, where the Bischler mechanism could be excluded. When α -anilinophenylacet-*p*-chloroanilide, $\text{NHPh}\cdot\text{CHPh}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\text{Cl}$, is heated at 200° with *p*-toluidine hydrobromide in *p*-toluidine, the aniline residue only is displaced; here the Bischler intermediate would be a tautomeric amidine, $\text{NHPh}\cdot\text{CHPh}\cdot\text{C}(\text{NPh})\cdot\text{NH}\cdot\text{C}_6\text{H}_4\text{Cl} \rightleftharpoons \text{NHPh}\cdot\text{CHPh}\cdot\text{C}(\text{NHPh})\cdot\text{N}\cdot\text{C}_6\text{H}_4\text{Cl}$, and its formation and decomposition would lead to extensive displacement of chloroaniline also. The high temperature necessary for the reaction, however, forbids the inference that a direct displacement is likely with arylamino-ketones at 120° . Under the same energetic conditions *p*-toluidine displaces aniline from benzylaniline; but benzhydryl-*p*-toluidine, which might have been expected to be very reactive, was unaffected by aniline-aniline hydrobromide at 150° .

It would appear, in sum, that in presence of a base and its salt an arylamino-ketone can react in two independent ways : (a) according to the Bischler-Strain scheme made very probable by Julian and his co-workers, leading in appropriate cases to arylamine displacement, to indolisation, and possibly to rearrangement; and (b) a strictly intramolecular rearrangement, perhaps by the mechanism suggested above.

Initial material.	Action of base + salt at 120° :			Product of indolisation.
	NH_2Ph .	$\text{NH}_2\cdot\text{C}_6\text{H}_7$.	NHPhMe .	
$\text{R}\cdot\text{CH}\cdot\text{COPh}$ NHPh	Rearr.	Rearr. + Displ.	Rearr.	
$\text{R}\cdot\text{CH}\cdot\text{COPh}$ $\text{NH}\cdot\text{C}_6\text{H}_7$	Rearr. + Displ.	Rearr.	Rearr.	
$\text{R}\cdot\text{CH}\cdot\text{COPh}$ NMePh	Unch.	Unch.	Unch.	
$\text{R}\cdot\text{CO}\cdot\text{CHPh}$ NHPh	Unch.	Displ.		
$\text{R}\cdot\text{CO}\cdot\text{CHPh}$ $\text{NH}\cdot\text{C}_6\text{H}_7$	Displ.	Unch.		
$\text{R}\cdot\text{CO}\cdot\text{CHPh}$ NMePh	Unch.	Unch.	Unch.	

Indolisation.—The base (II) and its analogues, each heated at 190 – 200° with the corresponding arylamine and its hydrobromide, yielded indoles; in all cases the product was that which would have resulted from the direct dehydration of an arylaminobenzyl *p*-anisyl ketone (as

(III), the stable type when simple rearrangement can be effected. Attempted indolisation of (II) and of its *p*-toluidino-analogue in pyridine-pyridine hydrobromide gave as sole definable product a trace of nitrogen-free material, different in the two cases. This failure is not general (see Crowther, Mann, and Purdie, *loc. cit.*), and so not clearly significant as to the mechanism of Bischler synthesis. This investigation as a whole, however, shows that many of the anomalies recorded in this synthesis may be due to demonstrable transformations of the arylamino-ketones before cyclisation, and not to an *ortho*-migration as postulated by Crowther, Mann, and Purdie :



EXPERIMENTAL.

Rearrangement.—The following experiment is typical. Phenyl α -anilino-*p*-methoxybenzyl ketone (II) was heated with aniline (3 mols.) and aniline hydrobromide (0.5 mol.) at 115–120° for 3 hours. The mixture was treated with dilute hydrochloric acid and ether; the combined acid layers deposited long needles of the hydrochloride of (III), which with alcoholic ammonia gave the free base (85%), identified by mixed m. p. and by reduction to *p*-methoxyphenyl benzyl ketone. No unchanged (II) could be recovered.

The same result followed when (II) was boiled for 3 hours with pyridine hydrobromide in pyridine, or with pyridine hydrobromide or sulphate in *n*-butyl alcohol. It was recovered unchanged after 2.5 hours' heating with *p*-toluidine alone at 130°.

Phenyl *N*-methylmesidino-*p*-methoxybenzyl ketone, prepared from the related bromo-ketone and methylmesidine (Ullmann, *Annalen*, 1903, **327**, 110) in the usual way (Cowper and Stevens, *loc. cit.*), crystallised from alcohol in colourless needles, m. p. 89–90° (Found: N, 4.0. $C_{25}H_{27}O_2N$ requires N, 3.8%). It was unchanged after 5–6 hours' heating with methylmesidine and its hydrobromide at 170°; after 6 hours at 190° the only isolable product was a little nitrogen-free material, white, glittering laminae from alcohol, m. p. 96–98°.

Displacement.—Phenyl α -anilino-*p*-methoxybenzyl ketone (II) or *p*-methoxyphenyl α -anilino benzyl ketone (III) was heated at 115–120° for 3 hours with *p*-toluidine (3 mols.) and *p*-toluidine hydrobromide (0.5 mol.). Fractional crystallisation of the product from alcohol yielded in each case 75% of *p*-methoxyphenyl α -*p*-toluidinobenzyl ketone, m. p. and mixed m. p. 141–142°, and 25% of material, m. p. 115–117°, indistinguishable from a mixture of the toluidino-ketone with an equal quantity of (III).

Simultaneous Rearrangement of (II) and Desylanthranilic Acid.—The acid, from benzoic acid and anthranilic acid (Weckowicz, *Ber.*, 1908, **41**, 4144), crystallised from alcohol in cream-coloured plates, m. p. 225–227° (Found: N, 4.4. Calc. for $C_{11}H_{11}O_3N$: N, 4.2%). Heated with aniline and aniline hydrobromide, it rapidly yielded desylaniline with some unchanged material. Equal weights of desylanthranilic acid and the ketone (II) were boiled for 3 hours in pyridine with pyridine hydrobromide. After addition of ether the filtered solution was extracted successively with sodium hydroxide solution and hydrochloric acid. The extracts yielded respectively desylanthranilic acid and the ketone (III), each in 90% yield, with no evidence of any other product. Three parts of (II) to one of desylanthranilic acid were used in another experiment with similar results. For comparison, phenyl α -(*o*-carboxyanilino)-*p*-methoxybenzyl ketone, $MeO \cdot C_6H_4 \cdot CHBz \cdot NH \cdot C_6H_4 \cdot CO_2H$, was prepared from benzanisoin and anthranilic acid: white needles, m. p. 198–199° (Found: N, 4.0. $C_{22}H_{19}O_4N$ requires N, 3.9%). With aniline and aniline hydrobromide it yielded (III).

“Direct” Displacement of Arylamine Residues.—Ethyl α -anilinophenylacetate (Stöckenius, *Jahresber.*, 1878, 780) was unaffected by boiling *p*-chloroaniline, but when *p*-chloroaniline and the ester were added successively to ethylmagnesium bromide in ether at room temperature (compare Hardy, *J.*, 1930, 398), α -anilinophenylacet-*p*-chloroanilide was obtained: long prisms from alcohol, m. p. 157–158° (Found: N, 8.6; Cl, 10.4. $C_{20}H_{17}ON_2Cl$ requires N, 8.3; Cl, 10.5%). The anilide was boiled for 3 hours with *p*-toluidine hydrobromide (0.5 mol.) in *p*-toluidine (3 mols.), and the mixture treated with ether and dilute hydrochloric acid. The tarry mass deposited by the acid layer afforded, after several crystallisations from ammoniacal alcohol, white needles, m. p. 183–185°. These were identical with α -*p*-toluidinophenylacet-*p*-chloroanilide, prepared in the same way as the anilino-compound (Found: N, 7.9. $C_{21}H_{19}ON_2Cl$ requires N, 8.0%). When methylaniline was used in place of *p*-toluidine, much non-basic material was formed and no individual product could be isolated.

Benzylaniline hydrobromide was boiled under reflux with *p*-toluidine (5 mols.) for 4 hours, and the basified mixture distilled in steam. The non-volatile material, with benzenesulphonyl chloride in pyridine, gave benzenesulphonbenzyl-*p*-toluidide (mixed m. p.) which depressed the m. p. of benzenesulphonbenzylanilide. Benzhydryl-*p*-toluidine (Busch and Rinck, *Ber.*, 1905, **38**, 1768) was unchanged by 3 hours' heating with aniline and aniline hydrobromide at 150°; treatment at 180–190° afforded an oil, b. p. 239–245°/15 mm., which gave no crystalline derivative.

Indolisation.—The ketone (II) was heated at 200° for 2.5 hours with aniline (3 mols.) and aniline hydrobromide (0.5 mol.), and the crude non-basic material distilled in a vacuum and crystallised from alcohol. 2-Phenyl-3-*p*-methoxyphenylindole (IV) formed colourless prisms, m. p. 188–190° (Found: N, 4.5. $C_{21}H_{19}ON$ requires N, 4.7%). The same product was obtained in small yield by heating (II) with pyridine hydrobromide (0.1 mol.) at 180° for 30 mins.; and was also synthesised by boiling with alcoholic hydrochloric acid phenyl *p*-methoxybenzyl ketone phenylhydrazone, prepared in alcohol-acetic acid as cream-coloured plates, m. p. 124–125° (Found: N, 8.7. $C_{21}H_{20}ON_2$ requires N, 8.8%).

The method first described was applied to the preparation of 2-phenyl-3-*p*-methoxyphenyl-5-methylindole, long prisms, m. p. 150–151° (Found: N, 4.8. $C_{22}H_{19}ON$ requires N, 4.5%), and of 2-phenyl-

3-*p*-methoxyphenyl-1-methylindole, needles, m. p. 131—133° (Found: N, 4.6%). The former was also synthesised by boiling phenyl *p*-methoxybenzyl ketone with *p*-tolylhydrazine in alcoholic hydrochloric acid for 3 hours; and for comparison 3-phenyl-2-*p*-methoxyphenylindole was prepared in like manner from *p*-methoxyphenyl benzyl ketone: needles, m. p. 140—142°, depressed by admixture with its isomeride (Found: N, 4.3%). The latter was synthesised by methylating (IV) as follows: To the indole (0.4 g.) in lukewarm acetone (6 c.c.) were added excess of powdered potassium hydroxide and, portion-wise, methyl sulphate (1 c.c.). After 45 mins., the mixture was treated with water, and the product extracted with benzene and crystallised from alcohol.

When (II) was heated with pyridine hydrobromide in pyridine in a sealed tube at 200°, the only isolable product crystallised from alcohol in nitrogen-free plates, m. p. 94—96°; the related *p*-toluidinoketone similarly gave a nitrogen-free substance, m. p. 92—94°, mixed m. p. with its analogue, 79—85°.

The authors are indebted to the Carnegie Trust for the Universities of Scotland for a Scholarship (to R. M. C.), and to Mr. J. M. L. Cameron for micro-analyses.

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[Received, November 4th, 1946.]

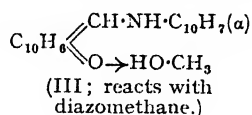
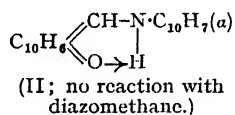
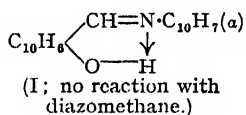
195. *Experiments with Diazomethane and its Derivatives. Part XIII.** *Action of Diazomethane on Hydroxyanils.*

By ALEXANDER SCHÖNBERG, AHMED MUSTAFA, and (in part) MUSTAFA KAMAL HILMY.

The *o*-hydroxyanils listed in Table I are *stable* or very resistant towards *ethereal* diazomethane solution, but, reacting in the ketonic form, they yield coumaran derivatives (listed in Table II) when treated with diazomethane *in the presence of methyl alcohol*; scheme (C) illustrates the proposed reaction mechanism. The stability towards *ethereal* diazomethane is believed to be due to the fact that in *ethereal* solution the anils do not contain a free hydroxyl group, but a chelate ring system (I or II), and that they react with methyl alcohol with formation of an intermolecular hydrogen bridge and the opening of the chelate ring system (III).

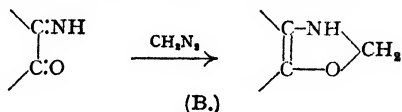
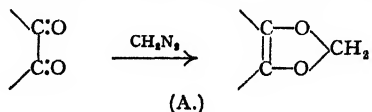
The importance of the above findings for the theory of chelation is stressed.

THIS paper deals with the remarkable behaviour of a number of anils (see Table I) derived from *o*-hydroxyaldehydes which were found to be stable towards diazomethane in *ethereal* solution, but reacted with it in the presence of methyl alcohol. By analogy with our previous findings (Schönberg and Mustafa, *J.*, 1946, 746), this is ascribed to the fact that these *o*-hydroxyanils are not true *o*-hydroxy-compounds but resonance hybrids having the hydrogen bridge (see I and II); when, however, methyl alcohol is present, the six-membered ring is opened and the ketonic



form (III) is established. The differential behaviour of substances listed in Table I towards diazomethane in *ethereal* and in *methyl-alcoholic* solution thus constitutes an additional criterion for the existence of chelation.

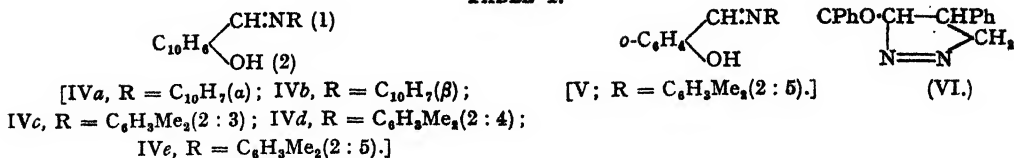
The anils mentioned above, in the presence of methyl alcohol, have the nature of compounds related to *o*-quinones and *o*-quinoneimines, which react with diazomethane to form five-membered heterocyclic compounds [see Arndt, Amende, and Ender, *Monatsh.*, 1932, 59, 202; Fieser and Hartwell, *J. Amer. Chem. Soc.*, 1935, 57, 1479; Schönberg and Mustafa, *loc. cit.*, in the case of (A), and Schönberg and Awad, *loc. cit.*, in the case of (B)]. By analogy, it would



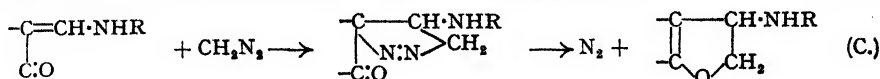
be expected that benzocoumaran derivatives should be obtained when (III) and its analogues are treated with diazomethane in the presence of methyl alcohol, and this is indeed the case (*e.g.*, formation of VIIa).

* For earlier papers (not numbered) by Schönberg and his co-workers on the action of diazomethane and its derivatives on organic substances, see *Ber.*, 1929, 62, 440, 1663; 1930, 63, 3102; 1931, 64, 1390, 2324, 2577; 1932, 65, 289; 1933, 66, 246; *Annalen*, 1930, 483, 176; *J.*, 1941, 348; *J.*, 1946, 746; this vol., in the press.

TABLE I.

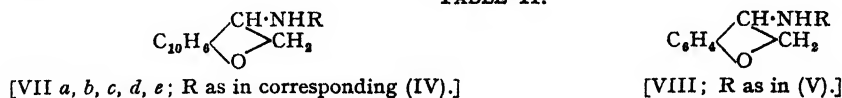


Mechanism of the Formation of the Coumaran Derivatives.—We believe that reaction occurs according to (C): similar schemes are proposed for the above-mentioned actions of diazomethane



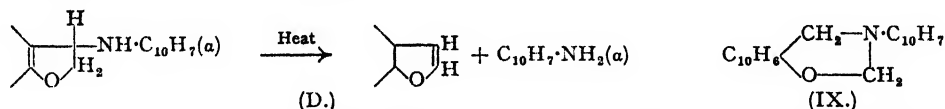
on *o*-quinones (1:2-diketones; *e.g.*, benzil) or *o*-quinoneimines; compare also the formation of (VI) from benzylideneacetophenone and diazomethane (Smith and Prings, *J. Org. Chem.*, 1937, 2, 23).

TABLE II.



Constitution of the Products listed in Table II.—These products are of an analogous structure; 3-(α -naphthylamino)-4:5-benzocoumaran (VIIa) is taken as an example. Its constitution is based on three facts: (a) the analogy of its formation (see A and B); (b) its properties; (c) the fact that no other formula can be proposed which fits the physical and chemical properties of the substance.

In contrast to (IVa), (VIIa) is colourless, in agreement with the proposed formula [reaction has taken place involving the chromophoric system in (III)]; (VIIa) has no methoxyl group and has one active hydrogen atom (the same holds true for all substances listed in Table II). When it is heated at 250°, it affords α -naphthylamine in addition to a resin, believed to be the polymerisation product of benzocoumarone (see D); the reaction product from (IVa) and diazomethane cannot therefore contain a tertiary nitrogen atom, for such a compound (*e.g.*, IX) cannot give α -naphthylamine on pyrolysis.



The compound (VIIa) was recovered unchanged when treated with phenylmagnesium bromide followed by hydrolysis; it does not react with diazomethane. The substances listed in Table II have basic properties; *e.g.*, 3-(*p*-2-xylyldino)coumaran (VIII) reacts with gaseous hydrogen chloride to form the corresponding hydrochloride. (VIIa) is completely different from the yellow 2-methoxynaphthylmethylene- α -naphthylamine (*O*-methyl ether of IVa); the nature of the latter is established by the fact that it is obtained by the action of methyl sulphate on the sodium salt of 2-hydroxynaphthylmethylene- α -naphthylamine (IVa) and by condensation of 2-methoxy-1-naphthaldehyde with α -naphthylamine. The same is true in the case of the β -naphthyl derivative (IVb). The substances listed in Table II are all solids, except (VIII), which was analysed as its hydrochloride.

Action of Diazomethane on the Anils of p-Hydroxyaldehydes.—It was found that 4-hydroxy-naphthylmethylene- α -naphthylamine and the corresponding β -naphthyl derivative react with diazomethane to form the known 4-methoxyl derivatives. This action took place even in ethereal diazomethane solution, which was to be expected since in these *p*-hydroxy-compounds the hydroxyl groups are free, no chelation being possible.

EXPERIMENTAL.

The ethereal diazomethane solution was prepared by the action of aqueous potassium hydroxide on nitrosomethylurethane followed by distillation (*Org. Synth.*, Vol. 15, p. 3).

Action of Ethereal Diazomethane Solution on p-Hydroxybenzylidene- α - and - β -naphthylamine.—These compounds (Senier and Forster, *J.*, 1914, 105, 2470) were converted into the corresponding *O*-methyl ethers by the action of an ethereal diazomethane solution in the cold (Found, respectively: C, 82.3;

H, 5.9; N, 5.7; and C, 82.5; H, 5.8; N, 5.8. Calc. for $C_{18}H_{18}ON$: C, 82.8; H, 5.7; N, 5.4%. Further identification was carried out by mixed m. p. determination with authentic specimens of *p*-methoxybenzylidene- α - (Pope and Fleming, *J.*, 1908, **93**, 1916) and β -naphthylamine (Steinhart, *Annalen*, 1887, 241, 341), respectively.

2-Hydroxy-1-naphthylmethylene-*o*-3-xylydine (IVc) was obtained by the condensation of equimolecular amounts of 2-hydroxy-1-naphthaldehyde and *o*-3-xylydine in yellow needles; m. p. 153° (Found: C, 83.1; H, 6.2; N, 5.3. $C_{18}H_{17}ON$ requires C, 82.9; H, 6.2; N, 5.1%). The condensation was carried out as described by Senier and Clarke (*J.*, 1911, **99**, 2084) for the synthesis of (IVd).

o-Hydroxyanils which resist the Action of an Ethereal Solution of Diazomethane.—Ethereal solutions of 1 g. each of (IVa) (Bartsch, *Ber.*, 1903, **36**, 1975), (IVb) (*idem*, *ibid.*), (IVc), (IVd) (Senier and Clarke, *loc. cit.*), (IVe) (*idem*, *loc. cit.*), and (V) were treated with excess of cold diazomethane (prepared from nitrosomethylurethane, 8 g.), and the mixture left for 48 hours at 0°. The ether was then evaporated off, and in every case the crude products showed the properties of the starting materials and after recrystallisation showed the same m. p. and mixed m. p.

Action of Diazomethane on *o*-Hydroxyanils in the Presence of Methyl Alcohol.—(a) 2-Hydroxy-1-naphthylmethylene- α -naphthylamine (IVa) (Bartsch, *loc. cit.*) (1 g.) in cold methyl alcohol (10 c.c.) was treated as in the preceding paragraph, fresh amounts of ethereal diazomethane being added during the 48 hours. The methyl alcohol and ether were evaporated off, and the solid residue was crystallised from benzene-light petroleum (b. p. 30–50°), forming colourless crystals, m. p. 169°. 3-(α -Naphthylamino)-4-5-benzocoumaran (VIIa) is insoluble in hot water, soluble in hot benzene, hot ethyl alcohol, and cold ether, and gives a yellow colour with concentrated sulphuric acid (Found: C, 85.4; H, 5.5; N, 4.2; active hydrogen, 0.34. $C_{22}H_{17}ON$ requires C, 84.9; H, 5.5; N, 4.5; active hydrogen, 0.32%). When crystallised from hot glacial acetic acid, it gave colourless crystals of the acetyl derivative, m. p. 225° (Found: C, 77.4; H, 5.9. $C_{24}H_{19}O_2N$ requires C, 77.6; H, 5.6%); when the solution of this derivative in hot water was treated with aqueous ammonia, (VIIa) was recovered (m. p. and mixed m. p.).

(b) Similarly, 3-(β -naphthylamino)-4-5-benzocoumaran (VIIb) was obtained from 2-hydroxy-1-naphthylmethylene- β -naphthylamine (IVb) in almost colourless crystals, m. p. 190°. It is soluble in hot benzene and ethyl alcohol and gives a yellowish-green colour when treated with concentrated sulphuric acid (Found: C, 84.8; H, 5.7; N, 4.5%). It was crystallised from benzene-light petroleum (b. p. 30–50°).

(c) The action of ethereal diazomethane in the presence of methyl alcohol on 2-hydroxy-1-naphthylmethylene-*o*-3-xylydine (IVc) gave colourless crystals of 3-(*o*-3-xylydino)-4-5-benzocoumaran (VIIc), readily crystallised from benzene, m. p. 173°; soluble in ether and hot ethyl alcohol, difficultly soluble in light petroleum (b. p. 50–60°) (Found: C, 83.1; H, 6.6; active hydrogen, 0.36. $C_{20}H_{15}ON$ requires C, 83.0; H, 6.6; active hydrogen, 0.35%).

(d) Similarly, 2-hydroxy-1-naphthylmethylene-*m*-4-xylydine (IVd) was treated with ethereal diazomethane in the presence of methyl alcohol, and 3-(*m*-4-xylydino)-4-5-benzocoumaran (VIId) obtained in colourless crystals; it is readily crystallised from benzene or methyl alcohol, m. p. 200°, difficultly soluble in ether, soluble in hot benzene (Found: C, 82.7; H, 6.2; N, 4.9. $C_{20}H_{15}ON$ requires C, 83.0; H, 6.6; N, 4.8%).

(e) In the usual manner (IVe) was converted into 3-(*p*-xylydino)-4-5-benzocoumaran (VIIe), which formed colourless crystals from benzene-light petroleum (b. p. 50–70°), m. p. 162–163° (yellow-brown melt), readily soluble in ether and benzene and difficultly soluble in light petroleum (b. p. 50–70°) (Found: C, 82.8; H, 6.1; N, 5.3; active hydrogen, 0.36%).

(f) Salicylidene-*p*-xylydine (V) (Senier and Shephard, *J.*, 1909, **95**, 443) was treated similarly; evaporation of the ether and methyl alcohol gave an oily product. Its ethereal solution on treatment with a stream of dry hydrogen chloride gave the hydrochloride of 3-(*p*-xylydino)-4-5-coumaran (VIII) in colourless crystals, m. p. 183° (not sharp); difficultly soluble in benzene and cold ethyl alcohol, soluble in hot water (Found: C, 69.9; H, 6.7; N, 5.1; Cl, 12.8. $C_{18}H_{15}ONCl$ requires C, 69.8; H, 6.5; N, 5.1; Cl, 12.8%).

Preparation of *o*-Methoxyanils.—The following *O*-methyl ethers of *o*-hydroxyanils were prepared by condensation of equimolecular amounts of 2-methoxy-1-naphthaldehyde (Barger and Stirling, *J.*, 1911, **99**, 2032) and the corresponding aromatic amine (cf. Steinhart, *loc. cit.*). The reaction mixture in alcohol was heated under reflux for 2 hours; on cooling, and if necessary on concentration, the methyl ethers of the hydroxyanils separated out. Colours obtained with concentrated sulphuric acid are given in parenthesis after the m. p.

2-Methoxy-1-naphthylmethylene- α -naphthylamine was obtained in brownish-yellow crystals from ethyl alcohol, m. p. 143–144° (red); it is readily crystallised from hot benzene (Found: C, 84.3; H, 5.6; N, 4.9; OMe, 9.4. $C_{22}H_{17}ON$ requires C, 84.9; H, 5.5; N, 4.5; OMe, 9.9%). The β -naphthyl analogue formed yellow crystals, readily crystallised from ethyl alcohol, m. p. 123° (reddish-orange) (Found: C, 84.3; H, 5.0; N, 4.8%). The *o*-3-xylydine compound formed yellow crystals from ethyl alcohol, m. p. 120° (orange-yellow), soluble in hot ethyl alcohol and benzene (Found: C, 83.2; H, 6.8; N, 4.7. $C_{20}H_{15}ON$ requires C, 83.0; H, 6.6; N, 4.8%). The *m*-4-xylydine analogue crystallised from methyl alcohol in yellow crystals, m. p. 71° (orange), easily soluble in benzene (Found: C, 83.1; H, 6.4; N, 4.8%). The *p*-xylydine compound formed yellow crystals from methyl alcohol, m. p. 117° (orange) (Found: C, 82.4; H, 6.8; N, 4.9%).

Action of Methyl Sulphate on 2-Hydroxy-1-naphthylmethylene- β -naphthylamine (IVb).—A suspension of (IVb) (1 g.) in hot methyl alcohol (15 c.c.) was treated gradually with methyl sulphate (about 2 c.c.), followed by addition of a methyl-alcoholic solution of potassium hydroxide till alkaline. The mixture was set aside at room temperature for 2 hours, poured into water, extracted with ether, and crystallised from ethyl alcohol; it formed yellow crystals, m. p. 123° (red-brown melt), not depressed when admixed with a specimen of 2-methoxy-1-naphthylmethylene- β -naphthylamine prepared as above. The α -analogue was similarly obtained in yellow crystals, m. p. 143°, not depressed when admixed with a specimen of 2-methoxy-1-naphthylmethylene- α -naphthylamine prepared as above.

Phenylmagnesium Bromide and 3-(α -Naphthylamino)-4-5-benzocoumaran.—The benzocoumaran

(VIIa) was treated with excess of phenylmagnesium bromide in ether-benzene, heated under reflux for 2 hours, and left overnight at room temperature. On hydrolysis, the starting substance was obtained unchanged or almost unchanged.

Action of Heat on 3-(α -Naphthylamino)-4:5-benzocoumaran.—The coumaran (VIIa) (1 g.) was heated in a stream of dry carbon dioxide for $\frac{1}{2}$ hour (bath temp., 250°). An almost colourless oil distilled over, which, on cooling, followed by extraction with hot light petroleum (b. p. 30–50°) and evaporation of the latter, gave colourless crystals of α -naphthylamine (m. p. and mixed m. p.). The part insoluble in the light petroleum was a resin which could not be identified.

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[Received, September 27th, 1946.]

196. *The Quantitative Determination of Galactose, Mannose, Arabinose, and Rhamnose.*

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Methods are described for the quantitative analysis of mixtures of galactose, mannose, arabinose, and rhamnose, which may occur amongst the hydrolysis products of plant gums. Galactose is estimated as its phenylmethylhydrazone, mannose as its phenylhydrazone, and arabinose as its benzoylhydrazone. The methods are accurate to within 9 mg. on weights above 0.1 g. Rhamnose can be determined as the benzoylhydrazone with an accuracy of ± 30 mg. on weights above 0.25 g.

THE plant gums are complex polysaccharides which contain a variety of sugar residues and amongst the products of hydrolysis galactose, mannose, arabinose, and rhamnose frequently occur. The quantitative determination of these sugars is a matter of some difficulty, the more so when they are admixed with other sugars and acids formed during the hydrolysis of the gums. We have carried out by the standard mucic acid method a large number of determinations of galactose in mixtures of sugars obtained from the hydrolysis of plant products, and have found the method inadequate, especially when only small quantities of material are available and when *d*-galacturonic acid and *l*-galactose are present. Other methods which have been described are (1) the fermentation method using special strains of yeast (Wise and Appling, *Ind. Eng. Chem. Anal.*, 1944, 16, 28), and (2) a method in which the insoluble phenylmethylhydrazone of galactose is weighed. This latter method has been used by Neuberg (*Biochem. Z.*, 1907, 3, 519), Lüdtké (*Biochem. Z.*, 1919, 212, 419), Neuberg and Schweitzer (*Monatsh.*, 1937, 71, 46), and Freeman, Challinor, and Willis (*Biochem. J.*, 1940, 34, 316). These authors converted pure galactose into its phenylmethylhydrazone under standard conditions and used a factor for the conversion of the weight of derivative isolated into the weight of galactose in solution. This method, however, gives accurate results only if the amounts of galactose in the control and in the unknown solution are identical. To avoid the necessity of carrying out a control estimation on each occasion we have determined the yields, under standard conditions, of the phenylmethylhydrazone of galactose obtained from various amounts of galactose (Table I). From the results a graph was constructed which showed that the relationship between galactose and the yields of galactose phenylmethylhydrazone was linear even when glucose, xylose, rhamnose, and glucuronic acid were present. Mannose and arabinose interfere with the estimation, but the difficulties thus arising can be readily circumvented. Mannose can be estimated by the phenylhydrazine method (Bourquelot and Herissey, *Compt. rend.*, 1899, 129, 339; see below) and can be removed by fermentation. Arabinose cannot be removed by fermentation but can be estimated by means of diphenylhydrazine (Neuberg, *Ber.*, 1900, 33, 2243; Wise and Paterson, *Ind. Eng. Chem.*, 1930, 22, 365) or by boiling with 12% hydrochloric acid and estimation of the furfural evolved. Since the precipitation of arabinose with phenylmethylhydrazine appears to be nearly quantitative in the presence of galactose, an estimate of the galactose present can be made after deducting the weight of phenylmethylhydrazone formed from the arabinose, the amount of which has been estimated by another method.

The quantitative estimation of arabinose in the presence of galactose is a matter of some difficulty since most reagents which give insoluble derivatives with arabinose also give insoluble derivatives with galactose, e.g., phenylmethylhydrazine and phenylbenzylhydrazine. A reagent which does not possess this disadvantage is benzoylhydrazone. This reagent also has the advantage of ease of preparation and of stability (Fischer and Paulus, *Arch. Pharm.*, 1935, 83; Militzer, *J. Chem. Educ.*, 1941, 25). In this estimation the mixture of sugars containing

arabinose (50 mg. in 500 mg.) is dissolved in water (2 c.c.) and a solution of benzoylhydrazine in alcohol (10 c.c.) is added; after two days the insoluble derivative is filtered off, dried, and weighed. Of many sugars examined the only one which interfered with this estimation was rhamnose, when present in quantities of over 300 mg. The standardisation was carried out as described above (see Table II *a* and *b*), and gave a method of estimating arabinose accurate to within 9 mg. on 100 mg. when using weights of arabinose above 0.1 g. In the absence of arabinose this reagent can be used for the characterisation and quantitative estimation of rhamnose (see Table III).

The estimation of mannose with phenylhydrazine has already been described (Bourquelot and Herissey, *Compt. rend.*, 1899, 129, 339). By adoption of the modified procedure described in the experimental section this method can be used for the estimation of mannose with an accuracy of approximately ± 3 mg. on quantities of 100 mg. and over of mannose. The method was standardised in a manner similar to that described for galactose and arabinose (Table IV), and it was found that no interference was caused by glucose, galactose, rhamnose, or arabinose.

EXPERIMENTAL.

Galactose. Reagent and Method of Analysis.—1-Phenyl-1-methylhydrazine (25 g.) was mixed with absolute alcohol (100 c.c.) containing glacial acetic acid (3 c.c.). The reagent was kept in a tightly stoppered brown glass bottle at 0°.

To the sugar sample (containing not more than 1.4 g. of sugars) dissolved in water (10 c.c.) the above reagent (10 c.c.) was added and the mixture was kept in a tightly stoppered flask at 33° for 12 hours with occasional shaking. It was then cooled to 0° for 9 hours and the crystals (m. p. 186°) were collected in a tared Gooch crucible, washed with ice-cold ethyl alcohol (10 c.c.), dried at 100° for 30 minutes, and weighed. The yields of phenylmethylhydrazone obtained from various weights of galactose with and without the presence of other sugars are given in Table I. From these results it can be seen that the method is accurate to within ± 3 mg. on amounts above 0.1 g.

TABLE I.

Galactose (g.).	Sugars added (g.).	Yield of phenylmethyl hydrazone (g.).	Galactose (from graph) (g.).	Error (g.).	Error calc. on original wt. of galactose (%).
0.037	—	0.039	0.039	+0.002	+ 5.4
0.077	—	0.096	0.077	nil	nil
0.126	—	0.177	0.132	+0.006	+ 4.8
0.260	—	0.367	0.263	+0.003	+ 1.2
0.426	—	0.615	0.433	+0.007	+ 1.7
0.711	—	1.036	0.719	+0.008	+ 1.1
1.394	—	2.042	1.403	+0.009	+ 0.7
0.184	Mannose, 0.500	1.020 ¹	0.178	-0.006 ¹	- 3.3
0.231	Arabinose, 0.500	1.030 ²	0.204	-0.027 ²	-12.0
0.225	Xylose, 0.500	0.320	0.231	+0.006	+ 2.6
0.202	Rhamnose, 0.500	0.281	0.205	+0.003	+ 1.5
0.232	Glucuronic acid, 0.500	0.320	0.231	-0.001	- 0.5
0.296	Glucose, 0.500	0.405	0.289	-0.007	- 2.4

¹ 0.245 G. of mannose phenylmethylhydrazone.

² 0.283 G. of *l*-arabinose phenylmethylhydrazone.

From these figures the equation $y = 0.673x + 0.013$ can be deduced where y corresponds to the weight of galactose giving a weight x of phenylmethylhydrazone.

Arabinose. Reagent and Method of Analysis.—Benzoylhydrazine, recrystallised from water and having m. p. 112–113° (25 g.), was dissolved in 95% alcohol (500 c.c.) and the solution was kept in a stoppered bottle until required. The sugar sample containing between 50 and 500 mg. of arabinose was dissolved in water (2 c.c.) in a 50 c.c. stoppered flask, and the reagent (10 c.c.) then added. The mixture was kept with occasional shaking at 20° for 24 hours and then at -3° for 22 hours. The crystalline residue, m. p. 186–190° (decomp.), was collected in a tared Gooch crucible, washed with ice-cold alcohol (10 c.c.), dried at 100° for $\frac{1}{2}$ hour and weighed. It will be seen (Table IIa) that of the sugars glucose, mannose, xylose, galactose, glucurone, and rhamnose, only the last named interfered with the estimation and then only when present in amounts above 300 mg. The relationship between the weight of arabinose and the yield of derivative was linear and fitted the equation $y = 0.555x + 0.022$ where y is the weight of arabinose corresponding to a weight x of derivative isolated.

d-Arabinose benzoylhydrazone was prepared, as described above, from *d*-arabinose and benzoylhydrazine, m. p. 186° (decomp.). *d*-Glucose gave with benzoylhydrazine a derivative {m. p. 176–179° (decomp.), $[\alpha]_D^{20} + 15^\circ \xrightarrow{17 \text{ hrs.}} -23^\circ$ in water} which was much more soluble than the derivative of

arabinose and rhamnose; it did not interfere with the estimation of these two sugars (Found: C, 52.4; H, 6.0; N, 9.6. $C_{15}H_{18}O_6N_2$ requires C, 52.4; H, 6.0; N, 9.4%).

In the second method of estimation of arabinose, an aqueous solution of benzoylhydrazine saturated at 20° (ca. 4.3 g./100 c.c. of water) was used as a reagent. The derivative is more soluble in this reagent

but separates in a more easily filtered form. Since the reagent contains no alcohol, alcohol-insoluble materials such as oligosaccharides and the barium salts of uronic acids remain in solution during the reaction and do not contaminate the precipitate of arabinose benzoylhydrazone. The dry, water-soluble product to be analysed, containing between 50 and 150 mg. of arabinose, is dissolved in the reagent (5 c.c.) and kept at 30° for 48 hours and then cooled to 0° for 2 hours. The crystalline precipitate is filtered off, washed with 10 c.c. of 95% alcohol, and dried at 100° to constant weight. If the residue contains between 150 and 400 mg. of arabinose, more of the reagent (10 c.c.) is used. The derivative is isolated and weighed as above. From the results obtained the equation $y = 0.67x + 0.010$ can be deduced where y is the weight of arabinose required to give a weight x of derivative (see Table IIb).

TABLE IIa.

Arabinose (g.).	Other sugars (g.).	Derivative of arabinose.	Arabinose from equation.	Error (g.).	Error calc. on wt. of arabinose taken (%).
0.212	—	0.310	0.194	—0.018	—8.5
0.234	Rhamnose, 0.087	0.362	0.223	—0.011	—5.0
0.206	Galactose, 0.071	0.297	0.187	—0.019	—9.2
0.215	Mannose, 0.108	0.319	0.199	—0.016	—7.4
0.294	—	0.478	0.288	—0.006	—2.1
0.344	—	0.574	0.341	—0.003	—0.9
0.402	—	0.683	0.401	—0.001	—0.3
0.243	Glucurone, 0.240	0.376	0.231	—0.012	—5.0
0.257	—	0.435	0.264	+0.007	+2.8
0.389	Rhamnose, 0.332	0.656	0.386	—0.003	—0.8
0.347	—	0.592	0.351	+0.004	+1.2
0.410	Galactose, 0.175	0.701	0.411	+0.001	+0.3
0.447	—	0.768	0.449	+0.002	+0.5
0.483	—	0.827	0.481	—0.002	—0.4
0.055	—	0.054	0.052	—0.003	—5.5
0.072	—	0.083	0.068	—0.004	—5.6
0.107	—	0.162	0.112	+0.005	+4.5
0.178	—	0.297	0.191	+0.013	+7.4
0.154	—	0.254	0.163	+0.009	+5.8
0.198	—	0.337	0.209	+0.011	+5.6
0.055	Rhamnose, 0.350	0.234	0.152	+0.097	Interferes
0.236	Xylose, 0.331; Rhamnose, 0.041; Mannose, 0.080	0.389	0.238	+0.002	+0.9
0.120	Glucose, 0.372	0.174	0.119	—0.001	—0.8
0.120	Glucose, 0.371	0.166	0.114	—0.006	—5.0
0.111	Mannose, 0.397	0.148	0.104	—0.007	—6.3
0.067	—	0.081	0.067	nil	nil
0.112	—	0.166	0.114	+0.002	+1.8
0.271	—	0.462	0.279	+0.008	+2.9
0.394	—	0.687	0.404	+0.010	+2.5
0.421	—	0.724	0.424	+0.003	+0.7
0.088	—	0.122	0.090	+0.002	+2.3
0.218	Mannose, 0.308	0.363	0.224	+0.006	+2.8
0.172	—	0.278	0.176	+0.004	+2.3
0.266	Rhamnose, 0.358	0.603	0.357	+0.091	Interferes
0.446	—	0.770	0.450	+0.004	+0.9
0.361	—	0.617	0.365	+0.004	+1.1
0.160	Xylose, 0.321	0.264	0.169	+0.009	+5.6
0.129	Galactose, 0.372	0.175	0.119	—0.010	—8.0

TABLE IIb.

Arabinose (g.).	Sugar impurity (g.).	Benzoyl-hydrazone found (g.).	Arabinose (from equation) (g.).	Error (g.).	Error calc. on wt. of arabinose taken (%).
0.068	—	0.062	0.052	—0.016	—23.5
0.079	—	0.088	0.069	—0.010	—12.7
0.116	—	0.164	0.120	+0.004	+3.4
0.185	—	0.286	0.202	+0.017	+9.2
0.213	—	0.314	0.220	+0.007	+3.3
0.173	Rhamnose, 0.190	0.202	0.147	—0.026	—15.0
0.268	—	0.389	0.271	+0.003	+1.1
0.384	Xylose, 0.190	0.559	0.385	+0.001	+0.3
0.412	—	0.625	0.428	+0.016	+3.9

Rhamnose.—Rhamnose cannot be so successfully estimated as arabinose by the use of benzoylhydrazine, owing to the greater solubility of the rhamnose derivative and the interfering effect of small

quantities of arabinose. The sugar sample (250 to 600 mg. in 2 c.c. water) was mixed with saturated alcoholic benzoylhydrazone solution (10 c.c.) and the solution kept at 30° for 41 hours. After 17 hours the solution was seeded with a trace of the rhamnose derivative. After 41 hours the solution was cooled to -3° and the product filtered off and washed with 95% alcohol (30 c.c. in all). To avoid charring it was necessary to dry the product first in a desiccator and then at 90° for 1 hour. From the yields of derivative (see Table III) the equation $y = 0.482x + 0.217$ was deduced, where y is the weight of rhamnose hydrate which will give a yield, x , of rhamnose benzoylhydrazone. The rhamnose benzoylhydrazone separated as very fine white crystals which could be recrystallised from methyl alcohol. The derivative separated from methyl alcohol as long white needles, m. p. 180° (decomp.) (Found: C, 55.5; H, 6.4; N, 10.0. $C_{13}H_{18}O_5N_2$ requires C, 55.3; H, 6.4; N, 9.9%).

TABLE III.

<i>l</i> -Rhamnose hydrate taken (g.).	Sugar impurity (g.).	Yield of benzoylhydrazone (g.).	Rhamnose hydrate (from equation) (g.).	Error (g.).	Error calc. on wt. of rhamnose taken (%).
0.578	—	0.679	0.544	-0.034	-5.9
0.451	—	0.529	0.471	+0.020	+4.5
0.349	—	0.351	0.386	+0.037	+10.7
0.210	—	0.026	0.230	+0.020	+9.6
0.270	—	0.191	0.309	+0.039	+14.4
0.322	—	0.271	0.347	+0.025	+7.8
0.370	—	0.326	0.374	+0.004	-1.1
0.408	—	0.385	0.379	-0.029	-7.1
0.470	—	0.471	0.444	-0.026	-5.5
0.503	—	0.481	0.449	-0.054	-10.7
0.213	—	0.002	0.218	+0.005	+2.3
0.338	—	0.234	0.330	-0.008	-2.4
0.256	—	0.086	0.258	+0.002	+0.8
0.251	—	0.162	0.295	+0.044	+17.5
0.310	Glucose, 0.470	0.257	0.341	+0.031	+10
0.464	—	0.467	0.442	-0.022	-4.7
0.554	—	0.605	0.508	-0.046	-8.3

Mannose. Reagent and Method of Analysis.—Phenylhydrazine (redistilled) (25 c.c.) was mixed with absolute alcohol (100 c.c.) containing glacial acetic acid (3 c.c.). The mixture was kept at 0° in a well-stoppered, dark bottle.

The sugar sample was dissolved in water (10 c.c.), the above reagent (10 c.c.) added, and the mixture kept in a well-stoppered flask at 32° for 15 hours, with occasional shaking. It was then cooled to 0° for 12 hours, and the phenylhydrazone was filtered off, washed with ice-cold alcohol (10 c.c.), dried at 100° for 30 minutes, and weighed. The yields of phenylhydrazone from various weights of mannose, together with the effect of various other sugars on the estimation, are given in Table IV.

TABLE IV.

Mannose (g.).	Sugar impurity (g.).	Yield of hydrazone (g.).	Mannose (from graph) (g.).	Error (g.).
0.026	—	nil	nil	-0.026
0.051	—	0.011	0.033	-0.018
0.100	—	0.114	0.100	nil
0.203	—	0.277	0.205	+0.002
0.401	—	0.573	0.400	-0.001
0.601	—	0.890	0.610	+0.009
1.001	—	1.488	1.003	+0.002
0.221	Glucose, 0.500	0.310	0.228	+0.007
0.260	Arabinose, 0.500	0.355	0.258	-0.002
0.214	Galactose, 0.500	0.300	0.220	+0.006
0.225	Rhamnose, 0.500	0.298	0.219	-0.006
0.205	Glucuronic acid, 0.500	0.280	0.207	+0.002

These figures fit the equation $y = 0.652x + 0.031$ where y is the weight of mannose giving a weight x of mannose phenylhydrazone.

From these results it can be seen that glucose, arabinose, galactose, rhamnose, and glucuronic acid do not interfere with the estimation of mannose, and that it is possible to carry out the estimation to within ± 3 mg. on amounts above 100 mg.

One of us (E. A. W.) wishes to thank The Khaki University of Canada for making arrangements which made it possible for him to take part in the work. We wish also to thank Imperial Chemical Industries Ltd. and Simon-Carves Ltd. for grants.

197. A Synthesis of Cytidine.

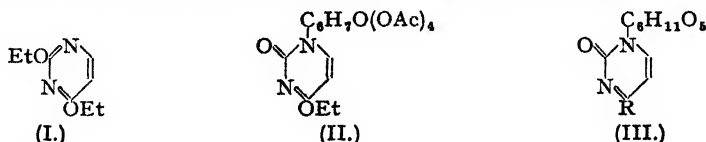
By G. A. HOWARD, B. LYTGOE, and A. R. TODD.

Hydrogenolysis of 1:2:3-triacetyl 5-trityl *d*-ribofuranose gives a syrupy 1:2:3-triacetyl *d*-ribofuranose converted on acetylation into the crystalline 1:2:3:5-tetra-acetyl *d*-ribofuranose. Treatment of the latter with liquid hydrogen bromide gave crude acetobromoribofuranose which was used directly to prepare *theophylline-7-β-d-ribofuranoside*. By reaction of the acetobromoribofuranose with 2:6-diethoxypyrimidine, followed by treatment of the product with methanolic ammonia, 3-β-*d*-ribofuranosidocytosine has been synthesised identical with the natural nucleoside, cytidine.

METHODS for the synthesis of nucleosides have been under investigation in this laboratory for some time with a variety of objects in view. On the one hand it was hoped that a successful outcome of the work would render available for biological examination a range of structural analogues of the natural nucleosides as a possible means of elucidating the mode of action of the latter in organised systems; on the other, study of the simpler compounds seemed a necessary preliminary to broader synthetic investigations relating to the co-enzymes and polynucleotides in the molecules of which nucleoside structures are preformed.

In a series of papers in this *Journal* ("Experiments on the Synthesis of Purine Nucleosides," Parts I—XVI, reviewed in *J.*, 1946, 647) we have reported progress made in the development of methods for the synthesis of analogues of adenosine, perhaps the most important of the natural nucleosides. General methods have been made available for the synthesis of 9-glycopyranosido- and 9-glycofuranosido-adenine derivatives, and answers have been provided to certain structural questions on which at the outset there was either no evidence or on which available evidence was not completely rigid. With the major problems of this part of the field approaching, as we hope, a satisfactory solution, it seemed desirable to broaden the scope of the investigations to include compounds of the type of guanosine, the pyrimidine ribosides, and the pyrimidine and purine deoxyribosides. The present communication records experiments which have led to the synthesis of the natural pyrimidine riboside, cytidine.

The problems of synthesis of pyrimidine glycosides have been examined by a number of previous workers. The route which has received most attention depends on the direct introduction of an acetylated glycosyl residue into the nucleus of an appropriate pyrimidine derivative by use of an acetohalogeno-sugar, a method essentially similar to Fischer and Helferich's synthesis of purine glycosides (*Ber.*, 1914, 47, 210). The early investigators (Fischer and Helferich, *loc. cit.*; Fischer, *Ber.*, 1914, 47, 1377; Levene and Sobotka, *J. Biol. Chem.*, 1925, 65, 469) employed, for glycosidisation, pyrimidine derivatives containing substituents such as hydroxyl, to which, as a result of their capacity for prototropic change, the glycosyl residue became attached, so that they were not successful in obtaining heterocyclic *N*-glycosides. This difficulty was overcome by Hilbert and his collaborators, employing 2:6-dialkoxy-pyrimidines, in which tautomerisation possibilities are excluded. Thus interaction of 2:6-diethoxypyrimidine (I) and acetobromoglucose gave the tetra-acetyl glucoside (II) which could be converted by methanolic hydrogen chloride into a 3-*d*-glucosidouracil (III; R = OH), or by methanolic ammonia into a 3-*d*-glucosidocytosine (III; R = NH₂) (Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, 52, 4489; Hilbert and Jansen, *ibid.*, 1936, 58, 60).



Structural analogues of (III) carrying various glycosyl residues have been obtained by this method (Hilbert, *ibid.*, 1937, 117, 331) including a 3-*d*-ribosidouracil (Hilbert and Rist, *J. Biol. Chem.*, 1937, 117, 331); all these compounds must, from their mode of preparation, be pyranosides.

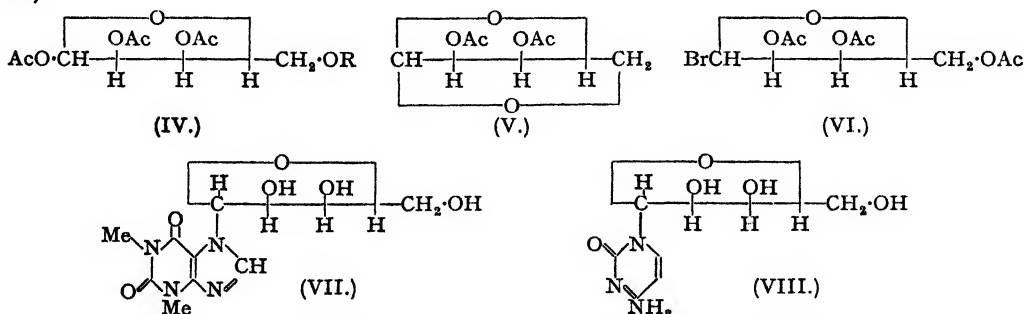
An alternative synthesis of pyrimidine nucleosides may be envisaged involving cyclisation of an appropriate glycosidamino-compound; such a method would be analogous in principle to our method for synthesis of purine-9-glycosides from 5-amino-4-glycosidaminopyrimidine derivatives. If developed, such a method might offer, in comparison with the synthesis from acetohalogeno-sugars, advantages such as the demonstration of the position of the sugar residue in the final product. It was in part this consideration that influenced us in our choice of a route for the synthesis of purine-9-glycosides, but it seemed of less importance in the case of the

pyrimidine nucleosides, since the N₃ location of the sugar residue in uridine has been fully established by Levene and Tipson (*J. Biol. Chem.*, 1934, **104**, 385), and we have shown (Davoll, Lythgoe, and Todd, *J.*, 1946, 833) that in the uracil-*d*-glucoside obtained by Hilbert's method the glucose residue does in fact, as formerly assumed from analogy (Hilbert and Johnson, *loc. cit.*), occupy the same position. We therefore decided in the first instance to attempt the synthesis of cytidine by extending Hilbert's method.

The acetohalogeno-ribofuranose required for this purpose belongs to a class of compounds which in spite of their potential synthetic value have been little explored, mainly because of the inaccessibility of suitable furanose intermediates. In the pentose series no true representative of this class has been obtained, and amongst the hexoses only those derived from galactose (Schlubach and Wagenitz, *Z. physiol. Chem.*, 1932, **213**, 87). Aniline-*d*-ribofuranoside (Berger and Lee, *J. Org. Chem.*, 1946, **11**, 75) seemed at first sight to be a suitable starting material for the preparation of acetobromoribofuranose. It has been stated (*idem, ibid.*; Berger, Solmsen, Leonard, Wenis, and Lee, *ibid.*, p. 91) that this compound can be acetylated to a 2 : 3 : 5-triacetyl *d*-ribosidoaniline which yields on careful acidic hydrolysis 2 : 3 : 5-triacetyl *d*-ribofuranose. However, as already recorded by us (Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 855) the acetylation is accompanied by a change to the isomeric pyranoside, so that in fact the product of the above reaction series is 2 : 3 : 4-triacetyl *d*-ribopyranose.

It was therefore decided to study in more detail the method used by Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) in their attempt to obtain acetobromoribofuranose. These investigators prepared 1 : 2 : 3-triacetyl 5-trityl *d*-ribose (IV; R = CPh₃), but attempts at selective removal of the trityl group from this compound were unsuccessful, giving instead of the desired 1 : 2 : 3-triacetyl *d*-ribofuranose (V; R = H) a diacetyl anhydribose <1 : 5> <1 : 4> (V) owing to simultaneous loss of the acetyl group at C₁. In these experiments hydrogen bromide in acetic acid or aqueous acetic acid was used for fission of the trityl ether linkage, but it is known (*e.g.*, Micheel, *Ber.*, 1932, **65**, 262) that the fission may be effected by hydrogenolysis. By using the latter method we were successful in preparing from (IV; R = CPh₃) a syrupy 1 : 2 : 3-triacetyl *d*-ribofuranose (IV; R = H), in which the terminal location of the free hydroxyl group was shown by its conversion into a syrupy tosyl derivative which readily exchanged its tosyl group for iodine in the Oldham-Rutherford reaction. Further acetylation of (IV; R = H) gave in good yield a crystalline 1 : 2 : 3 : 5-tetra-acetyl *d*-ribofuranose (IV; R = Ac). In order to convert this into acetobromoribofuranose we adopted the method used by Schlubach and Wagenitz (*loc. cit.*) for the preparation of acetobromogalactofuranose. Brief treatment of (IV; R = Ac) with liquid hydrogen bromide gave a syrup consisting essentially of the desired acetobromo-compound (VI); on account of its evident lability, isolation of the pure compound was not attempted, the crude product being used directly in glycosidation experiments.

When allowed to react with a suspension of theophylline silver in dry xylene, triacetyl theophylline-*d*-ribofuranoside was obtained as a gum, which on treatment with methanolic ammonia gave in good yield a crystalline theophylline-7-β-*d*-ribofuranoside (VII). The structure of this compound follows from the fact that it reacts with sodium metaperiodate, giving a crystalline α-theophylline-7-α'-hydroxymethylidiglycollic aldehyde identical with that obtained from similar oxidation of theophylline-7-β-*d*-glucopyranoside (Lythgoe and Todd, *J.*, 1944, 592).



These reactions provided satisfactory evidence of the nature of the crude acetobromoribofuranose and we could now proceed to the synthesis of cytidine (VIII). Interaction of 2 : 6-diethoxypyrimidine with (VI) at 65° gave a gummy product which on treatment with methanolic ammonia yielded a mixture of bases, from which cytidine was isolated by recrystallisation of the

picrates and finally of the sulphate. The cytidine sulphate so obtained agreed in composition and physical constants with that isolated from yeast nucleic acid. The Molisch test was negative, but after prolonged heating with the perchloric acid-tryptophan reagent (Cohen, *J. Biol. Chem.*, 1944, **156**, 691) the green colour characteristic of pentoses was slowly developed; natural cytidine sulphate behaved in the same manner. Final confirmation of the identity of the natural and synthetic products was obtained by comparison of their X-ray crystal photographs, for which we are indebted to Dr. Clews and Mr. Nicol of the Department of Crystallography.

The work described above represents the first synthesis of a naturally occurring nucleoside. Since it is known that cytidine can be deaminated to give uridine, the work also constitutes a synthesis of uridine, and provides confirmation of the degradative evidence relating to the structures of these two nucleosides.

EXPERIMENTAL.

1 : 2 : 3 : 5-Tetra-acetyl d-Ribofuranose.—1 : 2 : 3-Triacetyl 5-trityl d-ribofuranose (21 g.; Brederick, Köthnig, and Berger, *loc. cit.*) dissolved in glacial acetic acid (250 c.c.) was hydrogenated at 35° and atmospheric pressure in presence of Adams's palladium oxide (1 g.). After 3 hours 900 c.c. of hydrogen had been absorbed and the filtered solution was evaporated to dryness under reduced pressure. Crystallisation of the residue from alcohol gave triphenylmethane (8 g.), and the mother liquors after evaporation were dissolved in a little chloroform, light petroleum (b. p. 100–120°) was added, and the chloroform was removed by evaporation. The petroleum layer was removed, and the insoluble 1 : 2 : 3-triacetyl d-ribose acetylated in the usual way by acetic anhydride in pyridine. The acetylated material, isolated in the usual way, was dissolved in chloroform, washed with aqueous sodium bicarbonate and then with water, and the chloroform was removed from the dried solution under reduced pressure. Distillation of the residue at 100–110° (bath temp.)/10⁻⁴ mm. gave 1 : 2 : 3 : 5-tetra-acetyl d-ribofuranose as a syrup which crystallised on standing; m. p. 58°, $[\alpha]_D^{25} + 20^\circ (\pm 1^\circ)$ (c. 0.645 in chloroform). Yield, 9 g. (70%) (Found: C, 49.1; H, 5.7. $C_{13}H_{18}O_8$ requires C, 49.2; H, 5.2%).

Theophylline-7-β-d-ribofuranoside.—Pure anhydrous liquid hydrogen bromide (5 c.c.) was distilled into a Carius tube containing 1 : 2 : 3 : 5-tetra-acetyl d-ribose (1.5 g.) and, after being sealed, the tube was kept at room temperature for 10 minutes; dissolution was then complete. The tube was then opened and hydrogen bromide allowed to evaporate at room temperature, and the brown residue was evaporated twice with benzene under reduced pressure at 30° and finally heated to 35° in a high vacuum to remove hydrogen bromide as completely as possible. The crude acetobromoribofuranose so obtained was dissolved in a little xylene and the solution refluxed with a suspension of dry theophylline silver (1.5 g.) in dry xylene (50 c.c.) for 1 hour with exclusion of moisture. Silver bromide was removed from the hot solution, which was allowed to cool and filtered from a little theophylline which had separated. The filtrate was evaporated to dryness under reduced pressure and set aside for 2 days at 0° with methanolic ammonia. Removal of solvents and crystallisation of the residue from water gave theophylline-7-β-d-ribofuranoside as colourless needles, m. p. 189°, $[\alpha]_D^{25} + 27^\circ (\pm 5^\circ)$ (c. 0.257 in water) (Found in material dried at 100° and 0.1 mm.: C, 45.1; H, 5.5; N, 19.7. $C_{15}H_{18}O_8N_4$ requires C, 45.0; H, 5.0; N, 20.0%). Yield, 0.88 g. (60%).

Periodate Oxidation.—The above glycoside (209.2 mg.) was treated with a solution of sodium metaperiodate (208 mg. per 6 c.c. water) and set aside for 24 hours. The crystalline deposit of α-theophylline-7-α'-hydroxymethylidiglycolic aldehyde was collected (140 mg.), and had m. p. 205–206° (decomp.), $[\alpha]_D^{25} - 38^\circ$ (c. 0.21 in water) (Found: C, 43.7; H, 4.9. Calc. for $C_{12}H_{14}O_8N_4.H_2O$: C, 43.9; H, 4.9%). Lythgoe and Todd (*loc. cit.*) record for the same compound obtained from theophylline-7-β-d-glucopyranoside, m. p. 207–208° (decomp.), $[\alpha]_D^{25} - 42^\circ$.

In one experiment on the preparation of theophylline-α-d-ribofuranoside by the method described, there was isolated as sole product a substance separating from aqueous alcohol as colourless needles, m. p. 193°, $[\alpha]_D^{25} + 110^\circ$ (c. 0.254 in water) (Found: C, 45.8; H, 5.0; N, 17.9. $C_{15}H_{18}O_8N_4$ requires C, 46.2; H, 5.1; N, 17.9%). This substance required 1.06 mols. of periodate per mol. for complete oxidation, the oxidised product having $[M]_D^{25} 1.03^\circ (\pm 0.5^\circ) \times 10^4$. It seems possible that it may be theophylline-7-α-d-ribofuranoside.

Cytidine Sulphate.—Crude syrupy acetobromoribofuranose prepared in the manner described above from 1 : 2 : 3 : 5-tetra-acetyl d-ribose (5 g.) was dissolved in 2 : 6-diethoxypyrimidine (15 g.; Hilbert and Jansen, *J. Amer. Chem. Soc.*, 1935, **57**, 553) and the solution maintained at 65° for 24 hours with exclusion of moisture. After filtration from a little resin the solution was freed from excess of diethoxypyrimidine by evaporation at 100°/10⁻² mm. The residual 9 g. were dissolved in methanolic ammonia (40 c.c., saturated at 0°) and the solution was maintained at 80° for 4 days and then evaporated under reduced pressure. To a solution of the residue in hot alcohol (10 c.c.) hot alcoholic picric acid (5 g. in 50 c.c.) was added. The picrate separating on cooling was recrystallised from water, and then had m. p. ca. 150°. It was decomposed with dilute sulphuric acid, picric and sulphuric acids were removed in the usual manner, and the solution was concentrated to 5 c.c. After addition of concentrated sulphuric acid (0.7 c.c.) and alcohol (25 c.c.), inoculation with a trace of cytidine sulphate caused crystallisation. The product after recrystallisation from alcohol containing dilute sulphuric acid had m. p. 224° (decomp.) alone and in admixture with authentic material. $[\alpha]_D^{25} + 35^\circ$ (c. 0.366 in 1% aqueous sulphuric acid). Yield, 350 mg. [Found in material dried at 140°/0.1 mm.: C, 37.2; H, 5.2; N, 14.0. Calc. for $(C_8H_{12}O_5N_3)_2.H_2SO_4$: C, 37.0; H, 4.8; N, 14.2%].

We acknowledge gratefully a Maintenance Grant made to one of us (G. A. H.) by the Department of Scientific and Industrial Research.

198. The Constitution of Cherry Gum. Part II. The Products of Hydrolysis of Methylated Cherry Gum.

By J. K. N. JONES.

Methylated cherry gum has been hydrolysed and the following products of hydrolysis have been identified: 2:3:5-trimethyl *l*-arabinose, 2:5-dimethyl *l*-arabinose, 2:4:6-trimethyl *d*-galactose, 2:4-dimethyl *d*-galactose, 2:3:4-trimethyl *d*-glucuronic acid, and 2:3-dimethyl *d*-glucuronic acid. Derivatives of *d*-mannose and of *d*-xylose are also present but remain to be identified; other methylated derivatives of *d*-galactose may also be present.

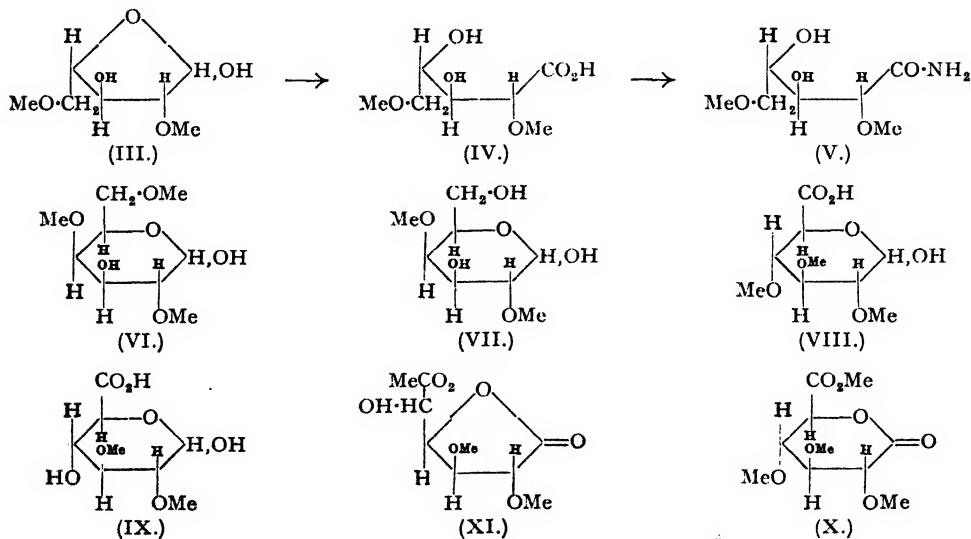
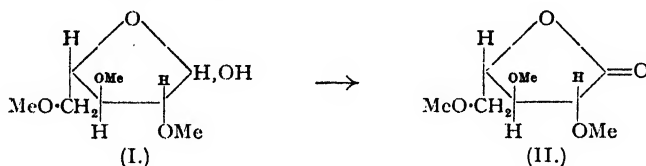
The results indicate the main structural features of the polysaccharide, but owing to the difficulty encountered in effecting the quantitative separation of these sugars it is not possible at this stage to suggest a unique structural formula.

It has been shown (Jones, *J.*, 1939, 558) that cherry gum contains the following sugars in the approximate proportions indicated: *d*-glucuronic acid (1 part), *d*-mannose (1 part), *d*-galactose (2 parts), *l*-arabinose (6 parts), and *d*-xylose (*ca.* 1.5%). The polysaccharide has now been converted into the fully methylated derivative by the thallium hydroxide method of methylation (Menzies, *J.*, 1926, 937; Hirst and Jones, *J.*, 1938, 502). This product is substantially homogeneous since no portions differing materially one from another were obtained on fractionation.

Methylated cherry gum, like methylated damson gum, readily underwent partial methanolysis with methyl alcoholic hydrogen chloride (2%) but there remained a resistant residue which required further prolonged boiling with this reagent before the reaction was complete. Six different sugars were recognised after fractional distillation of the methanolysis products, namely: 2:3:5-trimethyl *l*-arabinose, 2:5-dimethyl *l*-arabinose, 2:4:6-trimethyl *d*-galactose, 2:4-dimethyl *d*-galactose, 2:3:4-trimethyl *d*-glucuronic acid, and 2:3-dimethyl *d*-glucuronic acid. Derivatives of *d*-mannose and of *d*-xylose must be present, but their isolation has not yet been accomplished. It is possible that other methylated galactoses may also be present amongst the products of hydrolysis.

Proof of the identity of these sugar derivatives was obtained as follows:

(a) 2:3:5-Trimethyl *l*-arabinose (I) was identified after oxidation as crystalline 2:3:5-trimethyl *l*-arabonolactone (II).



(b) 2 : 5-Dimethyl *l*-arabinose (III) was recognised after oxidation as the crystalline lactone and amide (V) of 2 : 5-dimethyl *l*-arabonic acid (IV) (Smith, *J.*, 1940, 1035).

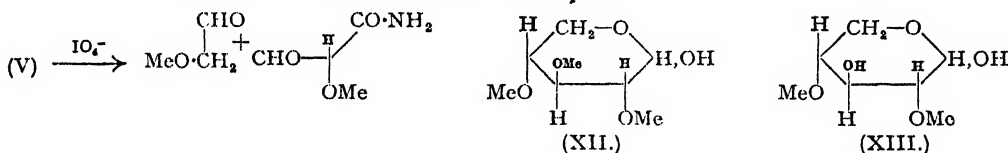
(c) 2 : 4 : 6-Trimethyl *d*-galactose (VI) was converted into its characteristic crystalline anilide (Bell and Wilson, *J.*, 1938, 1196; Percival and Somerville, *J.*, 1937, 1615).

(d) 2 : 4-Dimethyl *d*-galactose was isolated as crystalline 2 : 4-dimethyl *d*-galactose (VII) and its crystalline anilide (Smith, *J.*, 1940, 1050).

(e) 2 : 3 : 4-Trimethyl (VIII) and 2 : 3-dimethyl *d*-glucuronic (IX) acids were recognised as the corresponding crystalline derivatives of saccharic acid, *viz.* methyl 2 : 3 : 4-trimethyl *d*-saccharolactone ester (X) and methyl 2 : 3-dimethyl *d*-saccharolactone ester (XI).

Owing to the difficulty in identifying and separating quantitatively the various glycosides it is not possible to give a precise quantitative estimate of the various sugar derivatives formed on hydrolysis of the methylated polysaccharide. Hence no attempt is made to give a unique formula for cherry gum at this stage. However, a semi-quantitative examination of various sugar residues identified indicates that the ratio of trimethyl *l*-arabofuranose to 2 : 5-dimethyl *l*-arabinose is about 1 : 1 and that the ratio of 2 : 4 : 6-trimethyl *d*-galactose to 2 : 4-dimethyl *d*-galactose is also about 1 : 1.

An inspection of the constants for the pentose fractions shows that derivatives other than 2 : 3 : 5-trimethyl *l*-arabinose and 2 : 5-dimethyl *l*-arabinose must be present in them since both the free sugars and the lactones derived from the pentose fractions had optical rotations too high in the positive sense. 2 : 5-Dimethyl *l*-arabonic acid (IV) and its amide (V) possess hydroxyl groups on adjacent carbon atoms (C_3 and C_4) and should be oxidised by salts of periodic acid. Accordingly, fractions 23, 24, and 25 (see experimental section) were oxidised with periodic acid. From the product a lactone was obtained which must have possessed no α -glycol grouping, and since this lactone behaved as a pyranolactone it must be a derivative of 2 : 4-dimethyl (XIII) or 2 : 3 : 4-trimethyl *d*-xylose (XII) or 2 : 4 : 6-trimethyl *d*-galactose (VI). A pyranose derivative of *l*-arabinose is ruled out as it is known that all the arabinose units are in the furanose form (Jones, *loc. cit.*).



It has already been shown that 2-(*d*-glucuronosido)-*d*-mannose is part of both the damson gum and cherry gum molecules (Hirst and Jones, *J.*, 1938, 1174), and it is now obvious that both polysaccharides possess other points of similarity. For example, *d*-galactose units which are linked through positions C_3 and C_1 and C_6 , C_3 , and C_1 occur in both; in addition both molecules contain terminal *l*-arabinose and *d*-glucuronic acid units, and a *d*-glucuronic acid residue linked through C_1 and C_4 is common to both gums. A point of difference, however, is that in cherry gum *l*-arabinose residues occur which are linked through C_1 and C_3 (cf. gum arabic, Smith, *J.*, 1940, 1035) whilst in damson gum the linkage is through C_1 and C_5 .

It seems that cherry gum is built up on the same lines as damson gum (Hirst and Jones, *loc. cit.*) and gum arabic (Smith, *loc. cit.*) with probably a main chain of *d*-galactose units to which are attached side chains of aldobionic acids and pentose residues.

A complication arises from the fact that cherry trees may be grown as grafts on different stocks and it remains to be decided whether or not the chemical nature of the exuded gum is dependent upon the type of stock (private communication from F. W. Sansome). Although all the samples of cherry gum which have been examined possess very similar properties, until these points are investigated it cannot be claimed that the results now brought forward necessarily apply to all varieties of cherry gum.

EXPERIMENTAL.

Methylation.—The cherry gum (of English origin) had equiv. 1503, furfuraldehyde 31.8%, and $[\alpha]_D - 28^\circ$. It appeared to be identical with cherry gum obtained from the South of France which had equiv. 1487, furfuraldehyde 31.9%, and $[\alpha]_D - 28^\circ$ (mean values of determinations on seven separate nodules of gum). These figures are closely similar to those given in the literature for other samples of cherry gum isolated from widely different sources. Purified cherry gum (50 g.) (Jones, *J.*, 1939, 558) was dissolved in water (300 c.c.) containing a little *n*-thallous hydroxide, and a hot concentrated solution of thallous hydroxide (300 c.c. of 4*N*) was added with stirring. The precipitated thallium complex was rapidly filtered off, washed with methyl alcohol, and dried in a vacuum at 40° . The powdered thallium

derivative (120 mesh) was stirred with methyl iodide, with the exclusion of light and moisture, until the initial reaction had subsided, and the mixture was then boiled (under reflux) until the solid no longer gave an alkaline reaction (50 hours). Excess of methyl iodide was boiled off, the residue was exhaustively extracted with methyl alcohol, and the extracts were concentrated to a cream coloured solid (52 g.). This partly methylated derivative was dissolved in alcohol, and *n*-thallous ethoxide in benzene (300 c.c.) was added and the mixture evaporated to dryness with the exclusion of carbon dioxide. The solid was powdered (120 mesh), and boiled with methyl iodide until it no longer gave an alkaline reaction to litmus paper. The methylated product was extracted (as above) and the process of methylation with thallous ethoxide twice repeated. A final methylation with Purdie's reagents gave methylated cherry gum (48.0 g.); $[\alpha]_D^{20} = -28^\circ$ (*c.* 2.1 in methyl alcohol) (Found: equiv., 1650; OMe, 40.7%). This material (42 g.) was submitted to fractionation by precipitation from chloroform solution by addition of light petroleum. Three fractions were obtained as cream coloured solids, soluble in methyl alcohol, benzene, chloroform, acetone, dioxan, and cold water, insoluble in hot water and light petroleum. *Fraction R* (3.0 g.), $[\alpha]_D^{20} = -30^\circ$ (*c.* 1.4 in methyl alcohol) (Found: uronic anhydride (by boiling with 12% hydrochloric acid under the standard conditions), 10.1%; equiv. (by titration with 0.1*N*-sodium hydroxide), 1645; OMe, 39.0%). *Fraction S* (37.1 g.), $[\alpha]_D^{20} = -27^\circ$ (*c.* 2.4 in methyl alcohol) (Found: uronic anhydride, 10.4%; equiv., 1650; OMe, 42.4%). *Fraction T* (1.5 g.), $[\alpha]_D^{20} = -28^\circ$ (*c.* 0.9 in methyl alcohol) (Found: uronic anhydride, 10.3%; equiv., 1660; OMe, 40.1%). Calc. for fully methylated cherry gum: uronic anhydride, 10.1%; equiv. 1742; OMe, 42.7%.

Hydrolysis.—The methylated gum (*Fraction S*, 30 g.) was dissolved in 2% methyl alcoholic hydrogen chloride (300 c.c.) and boiled under reflux for 70 hours by which time $[\alpha]_D$ had changed from -27° to $+14^\circ$. The cooled solution was neutralised with silver carbonate, filtered, and evaporated to a syrup (34.4 g.), part of which was soluble in ether (A, 27.3 g., n_D^{20} 1.4545) and part insoluble (B, 7.1 g., n_D^{20} 1.4810).

The ether-soluble syrup (A, 27.3 g.) was heated to 90° with 0.3*N*-barium hydroxide (70 c.c.) for 15 hours, cooled, neutralised with carbon dioxide, and filtered, and the filtrate exhaustively extracted with chloroform in an all-glass apparatus. The chloroform extracts were evaporated to a syrup, n_D^{20} 1.4492, which on extraction with boiling ether gave a fraction soluble in ether (C, 17.45 g., n_D^{21} 1.4453) and an insoluble residue (D, 3.80 g., n_D^{21} 1.4624). The aqueous solution of the chloroform extraction was evaporated at $40^\circ/12$ mm. to a brown solid (E, 6.4 g.).

Fraction C (17.45 g.) was fractionally distilled in a vacuum, giving: *Fraction (1)*, 2:3:5-trimethyl methyl-*l*-arabofuranoside (7.80 g.), b. p. $110-120^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4380 (Found: OMe, 60.5%). *Fraction (2)*, a mixture of 2:3:5-trimethyl methyl-*l*-arabofuranoside and 2:5-dimethyl methyl-*l*-arabofuranoside (2.11 g.), b. p. $120^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4438 (Found: OMe, 58.3%). *Fraction (3)*, mainly 2:5-dimethyl methyl-*l*-arabofuranoside (5.14 g.), b. p. $125-140^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4532 (Found: OMe, 51.0%).

To the still residue was added *Fraction D* (3.80 g.) and the distillation continued. *Fraction (4)*, mainly 2:4:6-trimethyl methyl-*d*-galactoside (2.66 g.), b. p. $140-150^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4560 (Found: OMe, 50.4%). *Fraction (5)*, 2:4:6-trimethyl methyl-*d*-galactoside (0.85 g.), b. p. $150-160^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4618 (Found: OMe, 50.4%). This fraction partially crystallised. Still residue (F).

The ether-insoluble syrup B (7.1 g.) and the solid residue E (6.4 g.) were united and boiled with 2% methyl-alcoholic hydrogen chloride (300 c.c.) for 72 hours. The solution was neutralised with silver carbonate, filtered, and concentrated to a syrup which was heated with 0.3*N*-barium hydroxide (90 c.c.) for 12 hours. The cooled solution was neutralised with carbon dioxide, filtered, and exhaustively extracted with chloroform, and the extracts were concentrated to a syrup (G, 4.78 g., n_D^{19} 1.4730), which was added to the still residue (F) and the fractionation continued, giving: *Fraction (6)*, mainly 2:3:5-trimethyl methyl-*l*-arabofuranoside (1.278 g.), b. p. $110^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4372 (Found: OMe, 58.0%). *Fraction (7)*, a mixture of 2:5-dimethyl methyl-*l*-arabofuranoside and 2:4:6-trimethyl methyl-*d*-galactoside (0.70 g.), b. p. $120-150^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4572 (Found: OMe, 52.3%). *Fraction (8)*, mainly 2:4-dimethyl methyl-*d*-galactoside (4.25 g.), b. p. $160^\circ/0.001$ mm. (bath temp.), n_D^{20} 1.4750 (Found: OMe, 38.4%). *Fraction (9)*, dimethyl and monomethyl methyl-hexosides (1.15 g.), b. p. $160-200^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4845 (Found: OMe, 31.7%). Still residue, (0.38 g.).

The aqueous solution from G was evaporated to dryness and the residual barium salts were boiled with 6% methyl alcoholic hydrogen chloride (200 c.c.) for 24 hours. The solution was neutralised with barium carbonate, filtered, and evaporated to a syrupy mass which was exhaustively extracted with acetone. Removal of the solvent at $40^\circ/12$ mm. gave a syrup (n_D^{21} 1.4722), part of which (3.80 g.) was separated into two fractions by extraction with ether. The ether-soluble material (2.90 g., n_D^{19} 1.4625) was fractionally distilled in a vacuum, giving: *Fraction (10)*, mainly the methyl ester of 2:3:4-trimethyl methyl-*d*-glucuronoside (1.63 g.), b. p. $120^\circ/0.001$ mm. (bath temp.), $n_D^{19.5}$ 1.4530 (Found: OMe, 55%). This fraction was partially crystalline. *Fraction (11)*, mainly the methyl ester of dimethyl methylglucuronoside (0.83 g.), b. p. $150^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4681 (Found: OMe, 48.7%). To the still residue was added the ether-insoluble portion (0.90 g.) of the glucuronic acid fractions and the distillation was continued, giving: *Fraction (12)*, a mixture of the methyl esters of 2:3:4-trimethyl methyl-*d*-glucuronoside and dimethyl methyl-*d*-glucuronoside (0.60 g.), b. p. $160-200^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4698 (Found: OMe, 48.8%).

Examination of the Various Fractions.—Fractions (1), (2), and (6) were combined (11.1 g.) and hydrolysed with 0.1*N*-sulphuric acid (90 c.c.) for $7\frac{1}{2}$ hours at 90° . $[\alpha]_D^{20} = -20^\circ$ (*c.* 11.1 in 0.1*N*-sulphuric acid, initial value); -20° ($1\frac{1}{2}$ hours); -10° ($3\frac{1}{2}$ hours); $\pm 0^\circ$ ($7\frac{1}{2}$ hours, constant value). The solution was neutralised with barium carbonate, filtered, and evaporated to a syrup at $40^\circ/12$ mm., and the sugars were exhaustively extracted with chloroform. Concentration of the extracts gave a syrup (9.28 g., n_D^{19} 1.4522), a portion (8.68 g.) of which was fractionally distilled in a vacuum giving: *Fraction (13)* (7.40 g.), 2:3:5-trimethyl *l*-arabofuranose, b. p. $108-120^\circ/0.001$ mm. (bath temp.), n_D^{19} 1.4540; $[\alpha]_D^{20} \pm 0^\circ$ (*c.* 0.9 in water) (Found: OMe, 48.0. Calc. for $C_6H_{12}O_5$: OMe, 48.4%).

Fraction (14) (0.83 g.), b. p. 120–140°/0.001 mm. (bath temp.), $[n_D^{20}]$ 1.4668, $[\alpha_D^{20}] + 47^\circ$ (c, 0.55 in water) (Found: OMe, 42.8%). *Residue* (0.25 g.).

Fraction (13) (6.80 g.) was dissolved in water (20 c.c.) and oxidised with bromine (5 c.c.). The lactones (6.40 g.; n_D^{20} 1.4538) isolated in the usual manner were fractionally distilled giving *Fraction (15)*, mainly 2:3:5-trimethyl *l*-arabonolactone (2.5 g.), b. p. 104°/0.001 mm. (bath temp.), n_D^{20} 1.4452 (supercooled liquid), m. p. and mixed m. p. with an authentic specimen 27°, $[\alpha_D^{20}] - 28^\circ$ (initial value in water; c, 1.58); -29° (2 hours); -32° (4½ hours); -35° (6½ hours); -33° (22 hours); -32° (29½ hours); -31° (49 hours) (Found: equiv., 198; OMe, 48.3%). With liquid ammonia the lactone gave in good yield 2:3:5-trimethyl *l*-arabonamide, m. p. and mixed m. p., 138°. *Fraction (16)* (1.93 g.), mainly 2:3:5-trimethyl *l*-arabonolactone, b. p. 104–124°/0.001 mm. (bath temp.), n_D^{20} 1.4500, $[\alpha_D^{20}] + 8^\circ$ (c, 1.8 in water, initial value); -2° (1 hour); -17° (4 hours); -19° (6 hours); -26° (22 hours); -25° (33 hours); -24° (49 hours) (Found: equiv., 198; OMe, 51.0%). With liquid ammonia this lactone gave 2:3:5-trimethyl *l*-arabonamide, m. p. 138° in 70% yield. Fractions (15) and (16) were both contaminated with a lactone which, from its rate of mutarotation, was a δ -lactone and which may have been a derivative of *d*-xylonic or *d*-galactonic acid. The residue (2.0 g.) is considered below.

Fractions (3), (4), and (7) were combined (8.40 g.) and hydrolysed with *N*-sulphuric acid (100 c.c.) during 7 hours at 90°. $[\alpha_D^{20}] + 21^\circ$ (initial value); $+55^\circ$ (½ hour); $+56^\circ$ (1½ hours); $+54^\circ$ (2½ hours); $+52^\circ$ (4 hours); $+48^\circ$ (7 hours, constant value). The solution was neutralised with barium carbonate, filtered, and evaporated, and the residual syrupy sugars (7.64 g., n_D^{20} 1.4740) were isolated in the usual manner and distilled, giving: *Fraction (17)* (2.29 g.), mainly 2:5-dimethyl *l*-arabinose, b. p. 128–133°/0.001 mm. (bath temp.), n_D^{20} 1.4668, $[\alpha_D^{20}] + 60^\circ$ (c, 0.96 in water) (Found: OMe, 41.4%). *Fraction (18)* (3.36 g.), b. p. 135°/0.001 mm. (bath temp.), n_D^{20} 1.4735, $[\alpha_D^{20}] + 36^\circ$ (c, 1.6 in water) (Found: OMe, 42.0%). *Fraction (19)* (1.07 g.), b. p. 140–170°/0.001 mm. (bath temp.), $[\alpha_D^{20}] + 39^\circ$ (c, 0.88 in water) (Found: OMe, 36.9%). *Residue* (0.73 g.).

Fractions (14), (17), (18), and (19) were combined (7.4 g.) and oxidised with bromine water. The lactones (6.60 g.) were isolated, combined with the residue (2.0 g.) from fractions (15) and (16), and fractionally distilled in a vacuum giving *Fraction (20)* (1.15 g.), 2:5-dimethyl *l*-arabonolactone admixed with some other lactone of higher positive rotation (2:4:6-trimethyl *d*-galactonolactone?), b. p. 130–140°/0.001 mm. (bath temp.), n_D^{20} 1.4562, $[\alpha_D^{20}] + 14^\circ$ (c, 1.25 in water, initial value); $+4^\circ$ (1½ hours); -12° (5½ hours); -16° (9 hours); -15° (22 hours) (Found: equiv., 187; OMe, 38.8%). Calc. for $C_7H_{12}O_6$: equiv., 176; OMe, 35.2%). With liquid ammonia the lactone gave 2:5-dimethyl *l*-arabonamide in good yield, m. p. and mixed m. p. with an authentic specimen, 131° (Smith, J., 1939, 751) depressed to 122° on admixture with 2:3-dimethyl *l*-arabonamide. 2:5-Dimethyl *l*-arabonamide gave a negative Weerman test.

Conversion of 2:5-Dimethyl l-Arabonamide into 2:5-Dimethyl l-Arabonolactone.—The amide (0.4 g.) was heated at 90° with excess of *N*-sodium hydroxide until ammonia was no longer evolved (2 hours). The solution was acidified with *N*-sulphuric acid and then extracted exhaustively with chloroform. Concentration of the chloroform solution gave a syrup (0.35 g.) which was distilled in a vacuum; b. p. 160°/0.3 mm. The product crystallised, had m. p. 60°, and was pure 2:5-dimethyl *l*-arabonolactone (Found: OMe, 35.0. Calc. for $C_7H_{12}O_6$: OMe, 35%). *Fraction (21)* (5.09 g.) was mainly 2:5-dimethyl *l*-arabonolactone, b. p. 150°/0.001 mm. (bath temp.), n_D^{20} 1.4642, $[\alpha_D^{20}] + 21^\circ$ (c, 1.97 in water, initial value); $+8^\circ$ (1½ hours); -8° (5½ hours); -11° (9 hours); -11° (22 hours); -10° (38 hours) (Found: equiv., 189; OMe, 35.3%). With liquid ammonia the lactone gave 2:5-dimethyl *l*-arabonamide, m. p. 131°, in 60% yield. *Fraction (22)* (1.50 g.), had b. p. 160–180°/0.001 mm. (bath temp.), n_D^{20} 1.4720 (Found: OMe, 32.8%), and gave no crystalline amide with liquid ammonia.

The non-crystalline amides from Fractions (15) and (16) were combined and heated with barium hydroxide in a stream of nitrogen until the solution was free from ammonia. Excess of barium hydroxide was removed by carbon dioxide and the filtered solution decomposed with the calculated quantity of *N*-sulphuric acid, filtered, and evaporated to a syrup. In a similar manner lactones were regenerated from fractions (20), (21), and (22). The lactones recovered from (15) and (16) were distilled in a vacuum, giving *Fraction (23)*, b. p. 120°/0.001 mm. (bath temp.), n_D^{20} 1.4550, $[\alpha_D^{20}] + 33^\circ$ (c, 0.84 in water); $+27^\circ$ (1 hour); $+14^\circ$ (2 hours); $+7^\circ$ (3½ hours); -5° (7 hours); -11° (11 hours); -11° (23 hours). (Found: equiv., 200; OMe, 46.4%). With liquid ammonia the lactone gave an amide from which a small amount (50 mg.) of 2:3:5-trimethyl *l*-arabonamide was isolated; m. p. 138°. The syrupy amide gave a negative Weerman reaction showing the absence of amides with hydroxyl groups on C_2 . The lactones from Fractions (20), (21), and (22) were fractionally distilled in a vacuum, giving: *Fraction (24)*, b. p. 160°/0.001 mm. (bath temp.), n_D^{20} 1.4648, $[\alpha_D^{20}] + 43^\circ$ (c, 2.35 in water; initial value); $+32^\circ$ (1 hour); $+18^\circ$ (2 hours); $+8^\circ$ (3½ hours); -4° (7 hours); -10° (22 hours) (Found: equiv., 184; OMe, 39.5%). With liquid ammonia this lactone gave a syrupy amide which gave a negative Weerman test. *Fraction (25)*, b. p. 160–170°/0.001 mm., n_D^{20} 1.4740, $[\alpha_D^{20}] + 14^\circ$ (c, 0.85 in water, initial value); $+8^\circ$ (1½ hours); $+0^\circ$ (2½ hours); -6° (12½ hours); -11° (25 hours); -7° (31½ hours) (Found: equiv., 186; OMe, 36.4%). This lactone reacted with liquid ammonia giving a syrupy amide which gave a positive Weerman reaction.

The non-crystalline amides (3.50 g.) from the above lactones [Fractions (23), (24), and (25)] were dissolved in water and excess of periodic acid added. The solution became hot, and an odour resembling that of acetaldehyde was detected; this reaction destroyed all the 2:5-dimethyl *l*-arabonamide present in the syrupy amides. The solution was neutralised with barium carbonate and filtered, and the filtrate concentrated at 40°/12 mm. The distillate had an aldehydic odour and reduced hot Fehling's solution. The residual syrup was dissolved in water and oxidised with bromine in the presence of barium carbonate until non-reducing to Fehling's solution. Bromine was removed by aeration, the filtered solution evaporated to dryness, and the residue boiled with 2% methyl alcoholic hydrogen chloride for 10 hours. Hydrochloric acid was removed with silver carbonate, and the filtered solution evaporated at 90°/760 mm., to a syrup which was distilled in a vacuum, giving: *Fraction (26)* (1.8 g.), b. p. 135–145°/0.001 mm. (bath temp.), n_D^{20} 1.4538, $[\alpha_D^{20}] + 50^\circ$ (c, 1.2 in water, initial

value); + 40° (1½ hours); + 23° (4 hours); + 15° (7 hours); + 11° (23 hours); + 11° (28 hours, constant value) (Found: equiv., 175; OMe, 47.9%). With liquid ammonia the distilled lactone gave no crystalline amide. As no dimethyl dimethoxysuccinate was isolated, it is inferred that 2 : 3-dimethyl arabinose and 2 : 3-dimethyl xylose are not present in Fractions (23), (24), and (25). Fraction (27) (0.8 g.), b. p. 145–165°/0.001 mm. (bath temp.), n_D^{25} 1.4628. $[\alpha]_D^{20} + 77^\circ$ (c, 1.0 in water, initial value); + 59° (2 hours); + 33° (5½ hours); + 23° (24 hours, constant value) (Found: equiv., 190; OMe, 45.7%). This fraction gave no crystalline derivative on conversion into the corresponding amide by solution in liquid ammonia. This amide and the amide from Fraction (26) gave no sodium cyanate with sodium hypochlorite, proving the absence of a hydroxyl group on C₂. 3 : 4-Dimethyl arabinose, 3 : 4-dimethyl xylose, and 3 : 4 : 6-trimethyl *d*-mannose are thus absent from this fraction.

Fraction (5) (0.82 g.) was dissolved in *N*-hydrochloric acid (20 c.c.) and heated at 90–95° for 3 hours. $[\alpha]_D^{20} + 90^\circ$ (initial value); + 77° (1 hour); + 69° (2½ hours, constant value). The solution was neutralised with silver carbonate, filtered and evaporated to a syrup (0.80 g.), n_D^{20} 1.4738. $[\alpha]_D^{20} + 75^\circ$ (c, 4.0 in water) (Found: OMe, 39.0%). The syrup (0.79 g.) on being refluxed with alcoholic aniline gave 2 : 4 : 6-trimethyl *d*-galactose anilide (0.47 g.), m. p. and mixed m. p. 179°. The non-crystalline anilide was heated with *N*-hydrochloric acid (10 c.c.) at 70° for 3 hours. The cooled solution was neutralised with silver carbonate, filtered, and exhaustively extracted with light petroleum, and the extracted solution evaporated to a syrup which did not crystallise. The recovered sugar was oxidised with bromine water and the lactone isolated as a syrup which gave with liquid ammonia a non-crystalline amide. The amide gave no sodium cyanate with sodium hypochlorite (Weerman reaction), proving the absence of a hydroxyl group on C₂ and therefore of a mannose derivative in this fraction (see Jones, *loc. cit.*). The yield of 2 : 4 : 6-trimethyl *d*-galactose anilide corresponds to the presence of 0.50 g. of 2 : 4 : 6-trimethyl *d*-galactose in this fraction.

Fraction (8) (4.19 g.) was dissolved in *N*-hydrochloric acid (50 c.c.) and heated at 90–95° for 4 hours. $[\alpha]_D^{20} + 74^\circ$ (initial value), rising to + 78° (constant value). The solution was neutralised with silver carbonate, filtered, and evaporated to a syrup (3.98 g.) which did not crystallise and had $[\alpha]_D^{20} + 85^\circ$ (in water) (Found: OMe, 25.2%). The sugar (3.50 g.) on being heated with alcoholic aniline gave 2 : 4-dimethyl *d*-galactose anilide (0.62 g.), m. p. and mixed m. p. with an authentic specimen 212°, and a syrupy anilide (Y). This corresponds to the presence of 1.08 g. of 2 : 4-dimethyl *d*-galactose in this fraction. The crystalline anilide was hydrolysed with *N*-hydrochloric acid at 90° for 2 hours, the cooled solution neutralised with silver carbonate, and filtered, aniline extracted with ether, and the aqueous solution evaporated to a syrup which crystallised on nucleation with the monohydrate of 2 : 4-dimethyl *d*-galactose; m. p. and mixed m. p. with an authentic specimen 105°. The sugar (0.30 g.) was oxidised with bromine water and the lactone of 2 : 4-dimethyl *d*-galactonic acid (0.20 g.) isolated as a syrup, $[\alpha]_D^{20} + 100^\circ \rightarrow + 40^\circ$ (60 hours, constant value), which on solution in liquid ammonia gave 2 : 4-dimethyl *d*-galactonamide (0.11 g.). $[\alpha]_D^{20} + 58^\circ$ (c, 1.1 in water); m. p. and mixed m. p. 164° (Found: OMe, 27.6. Calc. for C₈H₁₇O₆N: OMe, 27.8%).

The filtrate from the anilide (Y) was evaporated to a syrup and hydrolysed with *N*-hydrochloric acid, and the free sugar (2.35 g., n_D^{20} 1.4842) isolated in the usual manner. The sugar was boiled in 2% methyl alcoholic hydrogen chloride and the resulting glycosides isolated and distilled; b. p. 160–180°/0.002 mm. (bath temp.), n_D^{25} 1.4700 (Found: OMe, 41.7%). This substance which analysed as a dimethyl methylhexoside failed to give any crystalline products on hydrolysis.

Fraction (9) (0.91 g.) was hydrolysed with *N*-hydrochloric acid (30 c.c.) for six hours at 95°. $[\alpha]_D^{20} + 60^\circ \rightarrow + 85^\circ$ (constant value). The sugars (0.7 g.) isolated in the usual manner did not crystallise and no crystalline derivative could be isolated from them.

Fraction (10) (1.3 g.) was hydrolysed with boiling *N*-hydrochloric acid and the resultant 2 : 3 : 4-trimethyl *d*-glucuronic acid isolated. It was converted by oxidation with bromine water into 2 : 3 : 4-trimethyl *d*-saccharic acid which was isolated as follows. Bromine was removed mainly by aeration, the last traces being removed by the passage of sulphur dioxide. The solution containing the methylated derivative was then extracted exhaustively with chloroform and the extracts were concentrated to a syrup (1.1 g.) which was esterified by boiling with methyl alcoholic hydrogen chloride. The resultant dimethyl ester of 2 : 3 : 4-trimethyl *d*-saccharic acid was isolated and converted into the methyl ester of 2 : 3 : 4-trimethyl saccharolactone by distillation in a vacuum. The product (0.9 g.), n_D^{20} 1.4605, crystallised and was purified by recrystallisation from ether; m. p. and mixed m. p. with an authentic specimen 110°.

Fractions (11) and (12) were combined and a portion of the mixture (0.9 g.) was hydrolysed. The resultant mixture of 2 : 3 : 4-trimethyl *d*-glucuronic acid and 2 : 3-dimethyl *d*-glucuronic acid was oxidised and the product converted into the corresponding dimethyl esters of 2 : 3 : 4-trimethyl and 2 : 3-dimethyl *d*-saccharic acid as described above. Distillation of this mixture (0.6 g.) gave a fraction (0.2 g.), b. p. 140°/0.0 mm., n_D^{20} 1.4650, which crystallised in part and from which methyl 2 : 3 : 4-trimethyl *d*-saccharolactone, m. p. 110°, was obtained by tiling the crystals followed by recrystallisation of the product from ether. A higher boiling fraction (0.3 g.), up to 200°/0.01 mm., n_D^{20} 1.4730, crystallised on nucleation with methyl 2 : 3-dimethyl *d*-saccharolactone. The crystals were separated by tiling and were purified by recrystallisation from alcohol-ether; m. p. 101°—not depressed on admixture with an authentic specimen.

The author wishes to thank Professor E. L. Hirst, F.R.S., for his interest and advice.

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[Received, November 13th, 1946.]

199. Some Reactions and Derivatives of 6- and 7-Nitro-2-naphthylamines. Part II. Nitration and Diazo-coupling.

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The acetyl and toluene-*p*-sulphonyl derivatives of 6- and 7-nitro-2-naphthylamines nitrate in the 1-position, and the dinitro-compounds are highly resistant to further nitration. 6- and 7-Nitro-2-naphthylamines couple in the 1-position, and the resulting *o*-aminoazo-compounds are oxidised to triazoles. Replacement of the amino by the acetoxy-group in 6- and 7-nitro-*p*-nitrobenzeneazo-2-naphthylamines readily occurs by heating in glacial acetic acid with sodium nitrite.

FURTHER nitration of both the acetyl and the toluene-*p*-sulphonyl derivatives of 6- and 7-nitro-2-naphthylamines occurs in the 1-position only, and absence of nitration in the 3-position, as pointed out by Bell (*J.*, 1929, 2784) for the corresponding derivatives of β -naphthylamine, is now further emphasised.

It may be noted that the further nitration of six of the eight possible heteronuclear mononitrotoluene-*p*-sulphon-naphthalides has now been investigated, and whereas the four heteronuclear mononitro-2-naphthalides are only mononitrated in acetic acid medium with fuming nitric acid, both 5- and 6-nitro-1-naphthalides are simultaneously dinitrated. This is in contrast to the simultaneous dinitration of the unsubstituted 1- and 2-toluene-*p*-sulphon-naphthalides. Incidentally, however, the *m*-nitrobenzenesulphonyl derivatives of 8-nitro- and 1:6-dinitro-2-naphthylamines both afforded the 1:6:8-trinitro-derivative on further nitration (Bell, *loc. cit.*).

The constitutions of the 1:7-dinitroaceto- and 1:7-dinitrotoluene-*p*-sulphon-2-naphthalides were established by hydrolysis to the amine followed by its diazotisation and deamination to the known 1:7-dinitronaphthalene (cf. Hodgson and Birtwell, *J.*, 1943, 433).

6- and 7-Nitro-2-naphthylamines, used as second components, both couple in alcoholic acetic acid with diazotised amines in the 1-position as shown by oxidation of the resulting *o*-aminoazo-compounds to triazoles, by their resistance to acetylation, and by their diazotisation and conversion into a mixture of *o*-azonaphthol and *o*-azonaphthyl acetate by the sodium nitrite-glacial acetic procedure of Hodgson and Foster (*J.*, 1942, 435) [cf. also Morgan and Chazan (*J. Soc. Chem. Ind.*, 1922, 41, 1r) and Morgan and Gilmour (*ibid.*, p. 61r) who showed similarly that 5- and 8-nitro-2-naphthylamines coupled in the 1-position]. 6- and 7-Nitro-*p*-nitrobenzeneazo-2-naphthylamines behaved somewhat differently towards the Hodgson and Foster procedure (*loc. cit.*), the former being hydrolysed more readily to give predominant naphthol in the mixture of naphthol and naphthyl acetate obtained, whereas the latter afforded a good yield of the 7-nitro-1-*p*-nitrobenzeneazonaphthyl acetate. It is noteworthy that tar was absent in these decompositions, indicating ease of replacement of the amine by the acetoxy-group. Previously, Hodgson and Foster (*loc. cit.*) had found, for azo-dyes with unsubstituted β -naphthylamine as second component, that meta-directing groups in the first component promoted this replacement, so that evidence is now to hand of the same effect by the meta-directing 6- and 7-nitro-groups in the β -naphthylamine component.

In connection with the transmissions of effects from the 6- to the 2-position (cf. Robinson and Thompson, *J.*, 1932, 2015), it is of interest that 6-nitro-2-naphthol would not couple with diazotised *p*-nitroaniline in either ethanol or aqueous sodium carbonate solution, showing the deactivating effect of the 6-nitro- on the phenolic group, in the potential ionic quinonoid structure, in which the 1-position, instead of acquiring the anionoid activity requisite for coupling, becomes kationoid.

The claim of Friedländer and Littner (*Ber.*, 1915, 48, 330) to have prepared some 5-nitro-aceto-2-naphthalide from β -acetonaphthalide, and since disproved by Veselý and Jakeš (*Bull. Soc. chim.*, 1923, 33, 942), has erroneously been repeated in *Org. Synth.*, 1933, 13, 73.

EXPERIMENTAL.

Nitration of 7-Nitro-2-acetonaphthalide.—7-Nitro-2-naphthylamine (3 g.) was refluxed with glacial acetic acid (12 c.c.) and acetic anhydride (3 c.c.) for 10 minutes; on cooling, an almost quantitative separation of 7-nitro-2-acetonaphthalide was obtained, which, after recrystallisation from 50% ethanol, had m. p. 221°. This acetyl compound (3 g.) was added gradually to nitric acid (12 c.c., *d* 1.5) during 15 minutes (the temperature being kept below 20°), and, after being stirred for a further 15 minutes, the mixture was poured on ice and the precipitate of 1:7-dinitro-2-acetonaphthalide (3.5 g.) removed, washed with water, and dried; it crystallised from glacial acetic acid in pale yellow needles, m. p. 222°

(Found: N, 15.1. $C_{11}H_9O_2N_3$ requires N, 15.3%). Should the temperature be allowed to rise during nitration even as high as 60° for 5–10 minutes, some oxidation occurs although the final product is mainly 1:7-dinitro-2-acetonaphthalide.

1:7-Dinitro-2-naphthylamine was obtained when the acetyl derivative above (2.5 g.) was hydrolysed by refluxing with a solution of ethanol (25 c.c.) and 50% aqueous sulphuric acid (25 c.c.) for 45 minutes; after cooling, the separated 1:7-dinitro-2-naphthylamine (2 g.) was filtered off, washed with ethanol, and dried; it crystallised from 50% aqueous pyridine in golden yellow needles, m. p. 248–249° (Found: N, 18.1. $C_{10}H_7O_4N_3$ requires N, 18.0%). Deamination of the amine (1.5 g.) occurred when its solution below 20° in sulphuric acid (8 c.c., *d* 1.84) containing sodium nitrite (0.6 g.) was stirred gradually into glacial acetic acid (20 c.c.), the stirring continued for 30 minutes, red copper oxide (2–3 g.) added portionwise during 15 minutes, and the temperature allowed to rise to 40°. After being stirred for a further 1 hour, the mixture was poured on ice, the precipitate of 1:7-dinitronaphthalene filtered off, washed with water, dried, extracted with boiling ethylene dichloride, the solvent removed from the extract, and the 1:7-dinitronaphthalene purified by sublimation at 190–200°/15 mm.; m. p. and mixed m. p. with an authentic specimen, 156° (Vesely and Dvorák, *Bull. Soc. chim.*, 1923, **33**, 319, give m. p. 156°).

Nitration of 7-Nitrotoluene-*p*-sulphon-2-naphthalide.—A solution of the naphthalide (2.5 g.) in glacial acetic acid (20 c.c.) at 60° was treated first with a crystal of sodium nitrite and then with 7.5 c.c. of a solution made up of nitric acid (1 c.c., *d* 1.5) in glacial acetic acid (9 c.c.); nitration began when the temperature was raised to 65°, and for completion the mixture was kept at 90° for 5 minutes; on cooling, 1:7-dinitro-*p*-toluenesulphon-2-naphthalide (1.7 g.) crystallised out; after removal, it was washed with glacial acetic acid and ether, and dried. It crystallised from glacial acetic acid in bright yellow rectangular plates, m. p. 165–166° (Found: N, 11.0. $C_{17}H_{13}O_6N_3S$ requires N, 10.8%). On hydrolysis by dissolution (1 g.) in sulphuric acid (10 c.c., *d* 1.84) and heating for 5 minutes at 40°, 1:7-dinitro-2-naphthylamine was obtained and precipitated by pouring the mixture on ice, with subsequent treatment as above. Alternatively, the 1:7-dinitro-*p*-toluenesulphon-2-naphthalide was converted directly into 1:7-dinitronaphthalene by the Hodgson and Birtwell procedure (*loc. cit.*), but diazotisation had to be carried out carefully since hydrolysis and diazotisation followed rapidly.

Coupling with Diazo-compounds.—To a solution of the naphthylamine (0.01 g.-mol.) in ethanol (400 c.c.) containing sufficient sodium acetate for the replacement by acetic acid of all mineral acid involved, was added an aqueous solution of the diazonium salt (chloride or sulphate, 0.01 g.-mol.), prepared from *p*-nitroaniline, *p*-chloroaniline, or *p*-toluidine, from which free nitrous acid had been removed by urea. The mixture was stirred for 1 hour, and the azo-dye filtered off, washed with cold ethanol (50 c.c.) and hot water, dried, and crystallised from nitrobenzene (charcoal). All the azo-dyes now described were moderately soluble in boiling acetic anhydride or boiling glacial acetic acid, and resisted acetylation thereby even at 100°; they were only slightly soluble in boiling toluene or ethanol. The sequence of colours produced by concentrated sulphuric acid and subsequent dilution with water are recorded immediately after the m. p. The large amount of ethanol used for the couplings is necessary to prevent uncoupled amine from separating with the azo-dye.

6-Nitro-*p*-nitrobenzeneazo-2-naphthylamine formed micro-needles, m. p. 304° (sintered at 290°; blood-red, salmon-pink, brownish-red precipitate) (Found: N, 21.1. $C_{18}H_{11}O_4N_5$ requires N, 20.8%). 6-Nitro-1-*p*-chlorobenzeneazo-2-naphthylamine formed orange-red micro-needles, m. p. 261° (sintered at 245°; magenta, red to yellow-brown) (Found: N, 17.4. $C_{18}H_{11}O_2N_4Cl$ requires N, 17.15%). 6-Nitro-1-*p*-tolylazo-2-naphthylamine formed orange red micro-plates, m. p. 234° (mauve, magenta, reddish-brown, orange) (Found: N, 18.5. $C_{17}H_{14}O_2N_4$ requires N, 18.3%). 7-Nitro-1-*p*-chlorobenzeneazo-2-naphthylamine formed felted scarlet needles, m. p. 199° (magenta, purple, brown precipitate) (Found: N, 17.4. $C_{18}H_{11}O_2N_4Cl$ requires N, 17.15%). 7-Nitro-1-*p*-nitrobenzeneazo-2-naphthylamine formed very dark red almost black needles, m. p. 265–266° (crimson, reddish-blue) (Found: N, 21.1. $C_{18}H_{11}O_4N_5$ requires N, 20.8%).

Oxidation of Azo-dyes to Triazoles.—The dye (0.5 g.) was dissolved in boiling glacial acetic acid (30 c.c.), and a solution of chromium trioxide (0.5 g.) in water (1 c.c.) was added with caution to the stirred boiling mixture; the red colour disappeared, to be replaced by a white precipitate. On cooling and dilution with water, the triazole separated; it was filtered off, washed with hot water until the filtrate was colourless, dried at 100°, and recrystallised from hot nitrobenzene.

6-Nitro-1:2-naphtho-*p*-nitrophenyltriazole crystallised in flesh-coloured micro-plates, m. p. 288° (Found: N, 21.3. $C_{16}H_9O_4N_5$ requires N, 20.9%). 7-Nitro-1:2-naphtho-*p*-nitrophenyltriazole crystallised in flesh-coloured plates, m. p. 311–312° (sintered at 300°) (Found: N, 21.3. $C_{16}H_9O_4N_5$ requires N, 20.9%).

Reactions of 6- and 7-Nitro-1-*p*-nitrobenzeneazo-2-naphthylamines with Sodium Nitrite in Glacial Acetic Acid.—(a) The 6-nitro-compound (1.0 g.) was dissolved in hot glacial acetic acid (350 c.c.) at 70°, and treated portionwise with finely powdered sodium nitrite (1 g.); nitrogen was briskly evolved, and, when the evolution had ceased, the solution was raised to the boil for 15 minutes. On cooling, no separation occurred, so water was added to precipitate the reaction product which was a mixture of difficultly separable 6-nitro-1-*p*-nitrobenzeneazo-2-naphthol and its acetate. When the precipitate (0.25 g.) was refluxed with ethanol (50 c.c.) containing hydrochloric acid (2 c.c., *d* 1.18) for 30 minutes, complete hydrolysis occurred, and the 6-nitro-1-*p*-nitrobenzeneazo-2-naphthol separated on cooling and was removed, washed, and dried; it crystallised from boiling glacial acetic acid in pillar-box red microcrystals, m. p. 314° (sintered at 305°; reddish salmon pink, orange-red) (Found: N, 16.7. $C_{16}H_{10}O_5N_4$ requires N, 16.5%), which were only slightly soluble in hot glacial acetic acid, almost insoluble in boiling ethanol, and readily soluble in boiling nitrobenzene. Alternatively, the dye (0.5 g.) was added gradually to a solution of sodium nitrite (0.15 g.) in sulphuric acid (4 c.c., *d* 1.84) at 0°, followed by the gradual addition of glacial acetic acid (5 c.c.) over 15 minutes below 20°. After a further 15 minutes ice chips were added and stirring maintained until evolution of nitrogen had ceased; on dilution with water 6-nitro-1-*p*-nitrobenzeneazo-2-naphthol separated.

(b) The 7-nitro-compound (1 g.) was dissolved in glacial acetic acid (200 c.c.), in which it is more soluble than the 6-nitro-isomeride, and treated as above so far as the boiling operation, when on cooling

there separated 7-nitro-1-p-nitrobenzenesazo-2-naphthyl acetate, which crystallised from boiling acetic acid in orange red needles, m. p. 233° (red violet, orange) (Found N, 15.0. $C_{18}H_{13}O_5N_4$ requires N, 14.7%). 7-Nitro-1-p-nitrobenzenesazo-2-naphthol was obtained by hydrolysis as above, and crystallised from boiling nitrobenzene in red micro-crystals, m. p. 310° (decomp.) (Found: N, 16.7. $C_{18}H_{13}O_5N_4$ requires N, 16.5%).

The authors are indebted to the Charles Brotherton Trust for a Research Scholarship (to E. R. W.), to Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals, and to Mr. Frank Hobson for micro-analyses.

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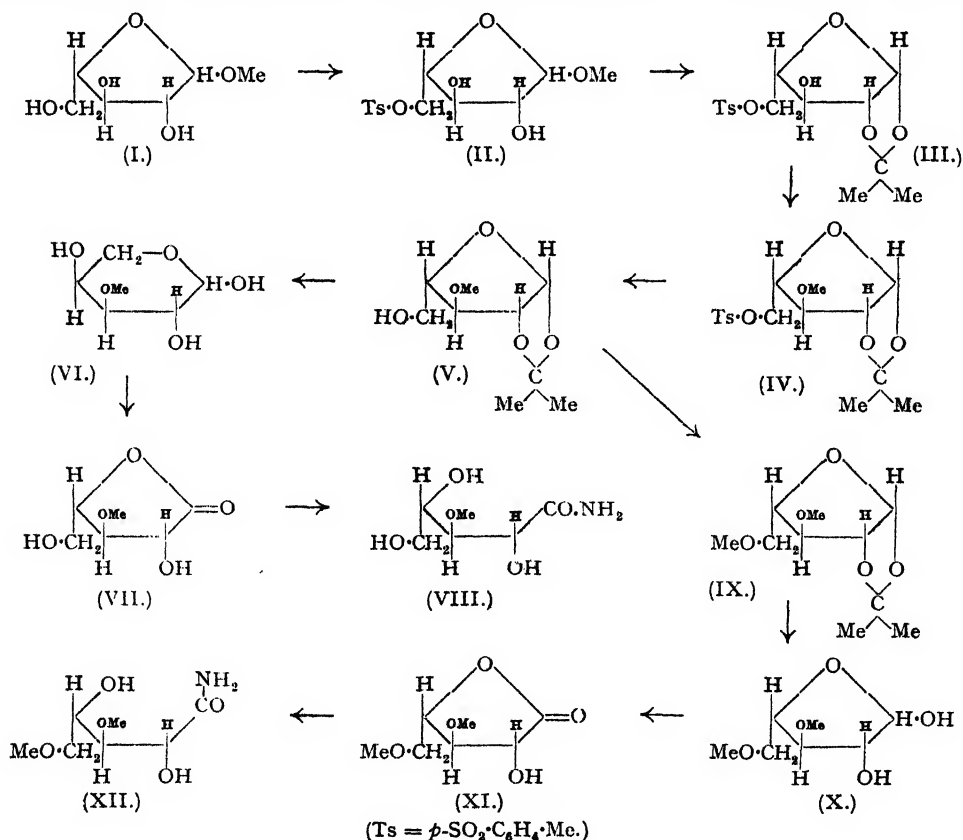
[Received, October 16th, 1946.]

200. The Synthesis of 3-Methyl and 3:5-Dimethyl 1-Arabinose.

By E. L. HIRST, J. K. N. JONES, and (Miss) E. WILLIAMS.

3-Methyl 1-arabinose has been prepared from 5-p-toluenesulphonyl 1:2-monoacetone l-arabinose. It forms a crystalline anilide and on oxidation gives 3-methyl 1-arabonolactone, further characterised as its crystalline amide. Methylation of 3-methyl 1:2-monoacetone l-arabinose gives 3:5-dimethyl 1:2-monoacetone l-arabinose which on hydrolysis yields the known 3:5-dimethyl l-arabinose (White, *J. Amer. Chem. Soc.*, 1946, 68, 272) which on oxidation gives 3:5-dimethyl l-arabonolactone, characterised as the crystalline amide and phenylhydrazide.

THE araban associated with pectin is known to be of the branched chain type (Hirst and Jones, *J.*, 1939, 454) since the methylated derivative gave on hydrolysis three products, namely, 2:3:5-trimethyl l-arabofuranose, 2:3-dimethyl l-arabinose, and a monomethyl derivative



the identity of which was not conclusively established though on the balance of evidence the methyl group was assigned tentatively to the 3-position. This monomethyl arabinose gave on

oxidation a furano-lactone, and since the free sugar had the properties of a derivative of arabopyranose it must be either 2- or 3-methyl 1-arabinose. The latter possibility was thought to be the correct one since the non-crystalline amide prepared from the crude lactone gave a positive Weerman reaction indicating the presence of an α -hydroxy-amide. The synthesis of 3-methyl 1-arabinose was accordingly undertaken in order to provide material of known constitution for comparison with that obtained from araban. The starting material in this synthesis was methyl 1-arabofuranoside (I) (Baker and Haworth, *J.*, 1925, 365) which was converted into the syrupy 5-*p*-toluenesulphonyl derivative (II) by reaction with the calculated quantity of *p*-toluenesulphonyl chloride in dry pyridine. The known 5-*p*-toluenesulphonyl 1 : 2-monoacetone 1-arabinose (III) [prepared previously from 1-arabinose diethylmercaptal (Compton and Levene, *J. Biol. Chem.*, 1936, 116, 189)] was then prepared from (II) by reaction with acetone containing hydrogen chloride. Methylation of (III) with silver oxide and methyl iodide gave 5-*p*-toluenesulphonyl 3-methyl 1 : 2-monoacetone 1-arabinose (IV) which on reductive alkaline hydrolysis (Compton and Levene, *loc. cit.*) gave 3-methyl 1 : 2-monoacetone 1-arabinose (V). On acidic hydrolysis this product was converted into syrupy 3-methyl 1-arabinose (VI). This compound formed a crystalline *anilide* on heating with alcoholic aniline and a crystalline *furanolactone* (VII) on oxidation with bromine water. A crystalline *amide* (VIII) was produced on reaction of the lactone with liquid ammonia (cf. Jellinek and Upson, *J. Amer. Chem. Soc.*, 1938, 60, 356). This amide depressed the melting point of 2-methyl 1-arabonamide and gave a positive Weerman test indicating the presence of a hydroxyl group on C2.

The monomethyl sugar isolated from the hydrolysis of peanut araban differs from 3-methyl 1-arabinose and must therefore be 2-methyl 1-arabinose. This has been subsequently confirmed by the synthesis of 2-methyl 1-arabinose which was found to be identical with the monomethyl sugar isolated from methylated peanut araban (forthcoming publications).

3-Methyl 1 : 2-monoacetone 1-arabinose (V) on further methylation gave 3 : 5-dimethyl 1 : 2-monoacetone 1-arabinose (IX) which on hydrolysis gave 3 : 5-dimethyl 1-arabinose (X); this on oxidation gave the corresponding furano-lactone (XI) which was smoothly converted into the α -hydroxy-amide (positive Weerman test) (XII) with liquid ammonia (cf. White, *loc. cit.*) and into the *phenylhydrazide* on heating with alcoholic phenylhydrazine.

EXPERIMENTAL.

5-*p*-Toluenesulphonyl Methyl-1-arabofuranoside and 5-*p*-Toluenesulphonyl 1 : 2-Monoacetone 1-Arabinose.—Methyl-1-arabofuranoside (31 g.) was dissolved in dry pyridine (250 c.c.) and *p*-toluenesulphonyl chloride (37 g.), dissolved in pyridine (50 c.c.), was added at 20°. Heat was evolved, and the solution was then left overnight (20 hours). Next morning pyridine was removed under reduced pressure at 60°, and the syrupy residue dissolved in chloroform and the solution washed successively with *n*-sulphuric acid, saturated sodium hydrogen carbonate solution, and water. The chloroform extract [dried (Na_2SO_4) and filtered] was then concentrated under reduced pressure to the syrupy 5-*p*-toluenesulphonyl methyl-1-arabofuranoside (36 g.). The syrup (30 g.), without further purification, was dissolved in acetone (300 c.c.) containing dry hydrogen chloride (3 g.). After 70 hours the acetone solution was poured into excess of sodium hydrogen carbonate solution and the arabinose derivative extracted with chloroform. Concentration of the chloroform extracts [dried (Na_2SO_4)] gave 5-*p*-toluenesulphonyl 1 : 2-monoacetone 1-arabofuranose, m. p. 130°, after recrystallisation from acetone-ether (yield, 21 g.) (cf. Compton and Levene, *loc. cit.*).

5-*p*-Toluenesulphonyl 3-Methyl 1 : 2-Monoacetone 1-Arabofuranose.—5-*p*-Toluenesulphonyl 1 : 2-monoacetone 1-arabofuranose (5 g.) was methylated by dissolution in methyl iodide (10 c.c.) and portionwise addition of silver oxide. The *product*, isolated in the usual manner, was recrystallised from acetone-light petroleum (b. p. 40–60°). The yield was quantitative, m. p. 101° (Found : C, 53.6; H, 6.1; OMe, 8.4; $\text{C}_8\text{H}_{12}\text{O}_7\text{S}$ requires C, 53.6; H, 6.2; OMe, 8.7%).

3-Methyl 1 : 2-Monoacetone 1-Arabofuranose.—5-*p*-Toluenesulphonyl 1 : 2-monoacetone 3-methyl-1-arabofuranose (4 g.) was dissolved in methyl alcohol (50 c.c.) and water (20 c.c.), and sodium amalgam (40 g., 4%) added with stirring at 30° (cf. Compton and Levene, *loc. cit.*). The resultant monoacetone derivative was extracted with chloroform and the extracts were dried (MgSO_4) and filtered. Removal of the solvent left crude 3-methyl 1 : 2-monoacetone 1-arabinose (1.8 g.), n_D^{20} 1.4565, which was purified by vacuum distillation; b. p. 120° (bath temp.)/2 mm., n_D^{20} 1.4572 (Found : C, 52.8; H, 7.5; OMe, 15.5. $\text{C}_8\text{H}_{12}\text{O}_6$ requires C, 52.9; H, 7.8; OMe, 15.2%).

3-Methyl 1-Arabinose.—3-Methyl 1 : 2-monoacetone 1-arabofuranose (0.73 g.) was dissolved in 20% acetic acid (20 c.c.) and boiled for 3 hours; $[\alpha]_D^{20}$ – 29° (initial value); + 95° (final value). The 3-methyl arabinose was isolated as a syrup on concentration of the solution in a vacuum; $[\alpha]_D^{20}$ + 110° (c, 3.6 in water) (Found : OMe, 19.2. $\text{C}_8\text{H}_{12}\text{O}_5$ requires OMe, 18.9%). On being heated with alcoholic aniline (180 mg.) the sugar (111 mg.) gave a crystalline *anilide* (100 mg.), m. p. 117° after recrystallisation from alcohol (Found : C, 60.1; H, 7.3; N, 5.9; OMe, 12.6. $\text{C}_{11}\text{H}_{17}\text{O}_4\text{N}$ requires C, 60.2; H, 7.1; N, 5.9; OMe, 13.0%).

No crystalline phenylhydrazone could be isolated. On oxidation of the sugar with bromine water under the usual conditions 3-methyl 1-arabofuranolactone was isolated as a crystalline solid (m. p. 71°) which was purified by sublimation in a vacuum, and then had m. p. 78° (constant value); $[\alpha]_D^{20}$ – 74° (c, 0.34 in water), no observable change in 24 hours (Found : C, 44.3; H, 6.7; OMe, 19.2; equiv., 162.

$C_6H_{10}O_5$ requires C, 44.4; H, 6.2; OMe, 19.1%; equiv., 162). With liquid ammonia the lactone gave 3-methyl *l*-arabonamide, m. p. 132°, after recrystallisation from alcohol-acetone (Found: C, 40.3; H, 7.3; N, 7.5; OMe, 17.1. $C_6H_{13}O_5N$ requires C, 40.2; H, 7.27; N, 7.8; OMe, 17.3%). This amide gave a positive Weerman test and depressed the m. p. of 2-methyl *l*-arabonamide.

3:5-Dimethyl Monoacetone *l*-Arabofuranose.—3-Methyl monoacetone *l*-arabinose (0.8 g.) was methylated with Purdie's reagents and the product (0.8 g.), isolated in the usual manner, was distilled under reduced pressure; b. p. 120° (bath temp.)/0.5 mm., n_D^{25} 1.4420 (Found: OMe, 28.1. $C_{10}H_{18}O_5$ requires OMe, 28.4%).

The above derivative (242 mg.) was boiled with 25% acetic acid (20 c.c.) for 3 hours; $[\alpha]_D^{20}$ — 39°, unchanged on heating. The solution was concentrated under reduced pressure and the resultant 3:5-dimethyl *l*-arabofuranose purified by solution in acetone followed by filtration. The sugar had n_D^{25} 1.4600 (Found: OMe, 34.6. Calc. for $C_7H_{14}O_5$: OMe, 34.8%).

The sugar (200 mg.) was oxidised with bromine (1 c.c.) in water (5 c.c.) at 20° for 24 hours. Excess of bromine was removed by aeration and the last traces of bromine by passage of sulphur dioxide. The lactone was then removed from the aqueous solution by continuous extraction with chloroform. Concentration of the extracts gave crystalline 3:5-dimethyl *l*-arabonolactone, m. p. 73° (after sublimation in a vacuum), depressed to 50° on admixture with 2:5-dimethyl *l*-arabonolactone; $[\alpha]_D^{20}$ — 83° (c, 0.12 in water), no observable change in 24 hours (Found: OMe, 33.9; equiv., 169. Calc. for $C_7H_{12}O_5$: OMe, 35.2%; equiv., 176). With liquid ammonia the lactone gave the corresponding amide, m. p. 144° (depressed to 120° on admixture with 2:5-dimethyl *l*-arabonamide), which gave a positive Weerman reaction (Found: C, 43.8; H, 7.6; N, 7.0; OMe, 31.2. Calc. for $C_7H_{15}O_5N$: C, 43.5; H, 7.8; N, 7.25; OMe, 32.1%).

The phenylhydrazide, m. p. 144° [depressed to 132° on admixture with the phenylhydrazide (m. p. 163°) of 2:5-dimethyl *l*-arabonic acid], was prepared by heating the lactone with an alcoholic solution of phenylhydrazine. It was recrystallised from acetone-ether (Found: C, 54.5; H, 6.8; N, 9.8; OMe, 21.6. $C_{13}H_{20}O_5N_2$ requires C, 54.8; H, 7.0; N, 9.9; OMe, 21.8%).

The authors thank Imperial Chemical Industries Ltd. for a grant.

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[Received, October 29th, 1946.]

201. The Constitution of Egg-plum Gum. Part I.

By E. L. HIRST and J. K. N. JONES.

The gum exuded on the bark of the egg-plum has been examined and shown to consist of *l*-arabinose (3 parts), *d*-xylose (1 part), *d*-galactose (3 parts), and *d*-glucuronic acid (1 part). The aldobionic acid which is present in the portion of the gum molecule more resistant to acidic hydrolysis is *d*-glucuronosido-6-*d*-galactose identical with the aldobionic acid component present in gum arabic. The oxidation of the gum with potassium periodate has been studied.

IN common with many other fruit trees of the family *Rosaceæ* the egg or yellow Pershore plum tree forms a gum during the months of August and September. The gums from several other trees have already been examined (see Hirst and Jones, *J.*, 1946, 506) and it was of interest to determine whether Pershore plum gum has a similar constitution. The gums obtained from exudation usually contain small amounts only of nitrogenous materials, which may be part of the enzyme system originally responsible for their synthesis (M. Stacey, private communication). They are salts of acidic polysaccharides, the acidity being due to the presence of *d*-glucuronic or *d*-galacturonic acids or of their methyl ethers. *d*-Galactose and *l*-arabinose appear to be invariable constituents, whilst *d*-mannose, *d*-xylose, and *l*-rhamnose have also been detected in some plant gums.

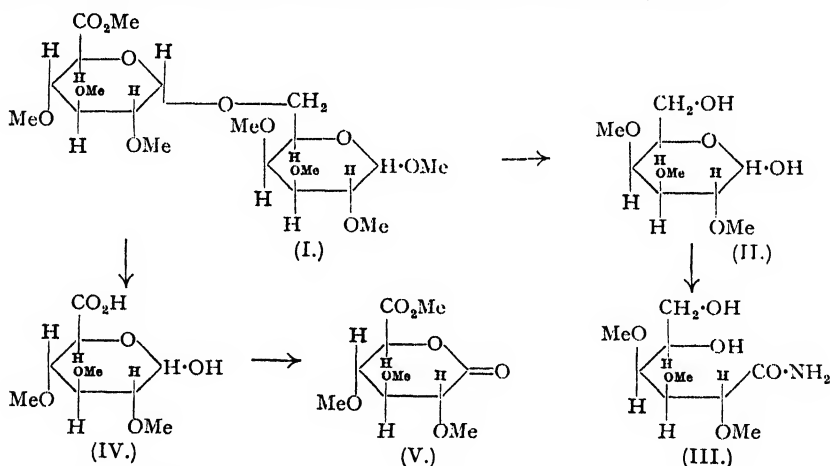
Purified ash-free Pershore plum gum is a white powder soluble in water giving an acidic solution which does not reduce Fehling's solution. So far as present evidence is available the gum so prepared appears to be a homogeneous substance, and attempts to extract from it by solvents fractions differing in elementary and physical properties have been unsuccessful. Gums obtained from several trees in the same area (Worcestershire) all have the same physical properties. The possibility remains, however, that the type of gum exuded by the tree may be dependent upon the type of stock on which the tree is grafted rather than upon the type of plum produced. Further work will be necessary before this can be settled.

The analytical figures for uronic acid residues (14.7%) and furfuraldehyde (25.5%) were obtained by boiling the polysaccharide with 12% hydrochloric acid and determining the amounts of carbon dioxide and furfuraldehyde formed. From these results estimates can be made of the pentose and the uronic acid content of the gum. An aqueous acidic solution of the ash-free polysaccharide undergoes graded hydrolysis on heating at 100°, the sugars obtained after hydrolysis consisting of a mixture of *l*-arabinose and *d*-xylose in the approximate proportion of 3 to 1. The remainder of the polysaccharide consists of *d*-galactose and *d*-glucuronic acid, since on

hydrolysis with *N*-sulphuric acid crystalline *D*-galactose is obtained together with an aldobionic acid having the structure *D*-glucuronosido-*D*-galactose (1 : 6 linkage) identical with the aldobionic acid in gum arabic. This structure, therefore, is an important feature in the mode of construction of the sugar residues in the repeating unit of the gum. It follows that Pershore plum gum resembles gum arabic, rather than damson or cherry gum (cf. Smith, *J.*, 1940, 1035), and in common with many other gums so far examined it contains a repeating unit consisting of two molecules of galactose united to an aldobionic acid. It is to be remembered, however, that owing to the difficulty encountered in isolating the aldobionic acid component of the gum in quantitative yield the possibility remains that some aldobionic acid other than 1 : 6-*D*-glucuronosido-*D*-galactose may be a component of the gum molecule. Conclusive proof is furnished below, however, of the presence of 1 : 6-*D*-glucuronosido-*D*-galactose as a part of the gum molecule.

The proof of the structure of the aldobionic acid follows from the observation that on methylation followed by hydrolysis of the methylated product (I), two products are obtained, namely, 2:3:4-trimethyl *D*-galactose (II), identified as its crystalline anilide and as the crystalline amide of 2:3:4-trimethyl *D*-galactonic acid (III), and 2:3:4-trimethyl *D*-glucuronic acid (IV), identified as the methyl ester of 2:3:4-trimethyl *D*-saccharolactone (V).

A quantitative estimation of the various sugars produced on hydrolysis of the original Pershore plum gum indicates that they were combined in the following proportions: *d*-glucuronic acid (1 part); *d*-galactose (3 parts); *l*-arabinose (3 parts); *d*-xylose (1 part).



When the gum is oxidised with potassium periodate under mild conditions, designed to prevent over-oxidation (see Brown, Dunstan, Halsall, Hirst, and Jones, *Nature*, 1945, **156**, 785) approximately one mol. of formic acid is produced and five mols. of periodate are consumed per equivalent of approximately 1220. The resulting oxidised polysaccharide, on being boiled under standard conditions with 12% hydrochloric acid, gives furfuraldehyde (10.8%) in a much diminished yield. This proves that some of those sugar residues in the original unoxidised polysaccharide which yield furfuraldehyde on distillation with hydrochloric acid have been destroyed during the oxidation. Since under the conditions of oxidation there is no continual rise in formic acid titre followed by a subsequent liberation of iodine, the glucuronic acid residue is not an end group (see Brown, Dunstan, Halsall, Hirst, and Jones, *loc. cit.*).

The oxidised polysaccharide on hydrolysis gives some *l*-arabinose (estimated as its benzoyl-hydrazone), but xylose could not be detected (see Breddy and Jones, *J.*, 1945, 738). The yields of *d*-galactose and *l*-arabinose indicated that at least 1.5 mols. of *d*-galactose and 0.5 mol. of *l*-arabinose per equivalent of 1220 are not oxidised by the periodate and therefore cannot possess adjacent hydroxyl groups in their combination in the gum molecule.

An examination of the product isolated from the reaction between the gum and triphenylmethyl chloride in pyridine shows that there are approximately four primary alcohol groups (Method of Linstead, *Arkiv Kemi, Min. Geol.*, 1945, 20 A, No. 13) per equivalent of 1220.

EXPERIMENTAL.

Purification of Egg-plum Gum.—The gum, which resembled damson and cherry gums in properties, was purified by precipitation with alcohol from aqueous solutions to which hydrochloric acid had been

added (for further details see Hirst and Jones, *J.*, 1938, 1177). The gum gave no precipitate with calcium or copper salts but gave a white precipitate on addition of a large excess of thallium hydroxide. It was unaffected by takadiastase and pectinase at pH 7 at 35°. Two samples were prepared: (A) from gum collected from several different trees in two orchards, (B) from gum collected off one tree (see Table).

	Gum A.	Gum B.
$[\alpha]_D^{20}$ (c, 2.4 as the sodium salt in water)	-27°	-25°
Equiv. (by titration with 0.1N-sodium hydroxide)	1228	1215
Furfuraldehyde	26%	25%
Uronic anhydride	—	14.7%
Galactan (from mucic acid determinations)	43%	44%

The samples from different trees are therefore substantially the same. The purified gum had a small iodine number (1.0 g. required 2.5 c.c. of 0.1N-iodine). [Found (crude gum): OMe, trace; N, nil.] The purified gum had a small methoxyl content (2.0%), probably owing to esterification during the purification process. Furfuraldehyde and uronic anhydride were determined after treatment of the purified polysaccharide with boiling 12% hydrochloric acid (Found: furfuraldehyde, 25.5; uronic anhydride or 2-ketohexonic acid, 14.7%). Methylpentose appears to be absent. [A substance yielding 14.7% of uronic anhydride or 2-ketohexonic acid and containing no other acidic residues should have an equivalent of 1197. Found by titration of the gum with alkali: equiv., 1222 (mean of two values).] This proportion of uronic anhydride accounts for 3.7% of the total furfuraldehyde, leaving 21.8% of furfuraldehyde contributed by the pentosan part of the polysaccharide, and since the greater part of the pentose present is *l*-arabinose (see below), the calculated anhydroarabinose content of the gum is approximately 44% (Calc. for a polysaccharide containing four pentosan units per repeating unit of equivalent 1190, 44.8%). Anhydrogalactose (estimated after oxidation to mucic acid), 43%.

Graded Hydrolysis of Egg-plum Gum.—(a) Egg-plum gum (50 g.) was heated with water (1½ l.) at 90–95°, the acidity of the solution being sufficient to bring about slow graded hydrolysis; the reaction was followed by polarimetric and iodometric observations: $[\alpha]_D^{20}$ -27° (initial value); -24° (40 mins.); -9° (3.1 hrs.); +32° (15.5 hrs.); +41° (22 hrs.); +47° (34 hrs.); +50° (50 hrs.). A much slower hydrolysis continued beyond this stage. The increase in iodine titre was followed by titration of portions of the solution with 0.1N-iodine by Baker and Hulton's method (*Biochem. J.*, 1920, 14, 754). Initial value (in c.c. 0.1N-iodine, calculated for 1 g. of gum) 2.5 c.c.; 6 c.c. (40 mins.); 15.5 c.c. (3.1 hrs.); 54 c.c. (15.5 hrs.); 58 c.c. (22 hrs.); 66 c.c. (34 hrs.); 72.6 c.c. (50 hrs.). The solution was evaporated at 40°/12 mm. to 500 c.c. and poured into alcohol (1½ l.); it then gave an alcohol-insoluble polysaccharide (A) (22.5 g.) which was washed with alcohol.

(b) *Reducing sugars obtained by graded hydrolysis.* The filtrate from (A) on concentration at 40°/12 mm. gave an acidic syrup which was dissolved in water, neutralised with barium carbonate, and filtered, and the filtrate poured into alcohol with stirring. The precipitated barium salt (B), which appeared to be the barium salt of the polysaccharide (A) which had escaped precipitation, was filtered off and the filtrate evaporated at 40°/12 mm. to a syrup which crystallised on standing. The crystalline solid (10.4 g.) was triturated with methyl alcohol and filtered off; it was identified as slightly impure *l*-arabinose, m. p. 154°; $[\alpha]_D^{20}$ +96° (c, 3.8 in water; equilibrium value); diphenylhydrazone, m. p. 194°. The filtrate from the crystalline solid on evaporation gave a syrup (C) (15.2 g.) which had $[\alpha]_D^{20}$ +38° and contained some oligosaccharide, since the iodine titre indicated the presence of only 9.3 g. of pentose. A furfuraldehyde determination indicated the presence of some 10.0 g. of pentose, whilst an arabinose estimation by means of diphenylhydrazine indicated the presence of approximately 5.0 g. of *l*-arabinose. Mucic acid was isolated after oxidation of a portion of the syrup with nitric acid, proving the presence of some 2.4 g. of galactose (free or combined). The syrup underwent further hydrolysis on heating with 0.5N-sulphuric acid for 1 hour. The optical rotation became constant at +60° and the iodine titre on a portion of the solution (A) showed that approximately 15 g. of reducing sugars were now present in solution. An estimation by means of diphenylhydrazine now showed the presence of 5.8 g. of *l*-arabinose, an increase of only 0.8 g. It can be inferred, therefore, that the oligosaccharide originally present contained *d*-galactose and *d*-xylose since the increase in reducing power of the solution is not due to increase of *l*-arabinose content but to an increase of *d*-galactose and *d*-xylose. A portion of the solution (A) after hydrolysis was neutralised with barium carbonate and filtered, and the filtrate evaporated to a syrup. *l*-Arabinose was removed from this syrup as its diphenylhydrazone, and the non-crystalline diphenylhydrazones remaining were then decomposed by warming with form aldehyde solution in the presence of acetic acid. The mixture was exhaustively extracted with ether and the aqueous solution evaporated to a syrup. [A portion of this gave the characteristic crystalline derivative of xylose, m. p. 210°, with a methyl alcoholic solution of benzaldehyde (see Breddy and Jones, *J.*, 1945, 738).] The syrup was boiled for 4 hours with 4% methyl alcoholic hydrogen chloride, and the solution was then neutralised with silver carbonate, filtered, and evaporated to a syrup which was methylated first by the thallium method (Menzies, *J.*, 1926, 937), and then with Purdie's reagents. The methylated sugars (4.0 g.) were distilled in a vacuum and gave a fraction (3.6 g.), b. p. 100° (bath temp.)/0.1 mm.; n_D^{18} 1.4438; $[\alpha]_D^{20}$ +53° in water. This fraction was hydrolysed with *N*-hydrochloric acid (50 c.c.) on the boiling water-bath. $[\alpha]_D^{20}$ fell from +53° to +44°. The free sugars were worked up in the usual manner and distilled in a vacuum; the distillate then crystallised. 2:3:4-Trimethyl *d*-xylose was recognised by its m. p. and mixed m. p. 91°, after recrystallisation from ether. The non-crystalline sugars gave some tetramethyl galactose anilide on heating with alcoholic aniline. This result, taken in conjunction with reducing values, furfuraldehyde yields, rotational values, and yield of *l*-arabinose diphenylhydrazone, indicates that the sugars produced on autohydrolysis consist of *l*-arabinose and *d*-xylose in the approximate proportion of three to one and that a small amount of galactose is also produced during the hydrolysis. A polysaccharide of equivalent weight 1222 and containing this amount of arabinose would yield 36.8% of arabinose on hydrolysis (Found: arabinose content, 32.4%).

(c) *Examination of the barium salt (B).* The barium salt (B) (10.4 g.) was obtained as a white powder

easily soluble in water, giving a yellow neutral solution, $[\alpha]_D^{20} +4^\circ$ (c. 3.3 in water). OMe, 3.0% (probably derived from adsorbed alcohol). It contained 11% of barium, gave 8.3% of furfuraldehyde on boiling with 12% hydrochloric acid, and on oxidation gave mucic acid equivalent to the presence of 50% of galactan. It was slightly reducing to Fehling's solution and reduced alkaline iodine (1 g. required 40.5 c.c. of 0.1N-iodine). On being heated with N-sulphuric acid for $3\frac{1}{2}$ hours the barium salt underwent hydrolysis with an increase in iodine titre; initial value (in c.c. of 0.1N-iodine per 1 g. of barium salt) 41 c.c.; 58 c.c. (1 $\frac{1}{2}$ hrs.); 65.4 c.c. (2 hrs.); 70.7 c.c. (3 hrs.); 74.4 c.c. (3 $\frac{1}{2}$ hrs., constant value). The change in rotation was not observable owing to the colour of the solution. The solution was neutralised with barium carbonate, filtered, and evaporated to a syrup, which was extracted with methyl alcohol. Concentration of the extracts gave a syrup which soon crystallised. Trituration with alcohol gave crystalline *d*-galactose, $[\alpha]_D^{20} +78^\circ$ in water, m. p. and mixed m. p. 164° , in 42% yield calculated on the weight of the syrup isolated. (6.65 G. of barium salt gave 2.7 g. of syrup.) The non-crystalline barium-free residue showed $[\alpha]_D^{20} +45^\circ$ (c. 1.22 in water) and was 50% galactose (calc. on the yield of mucic acid obtained after oxidation with nitric acid under standard conditions). Mannose appeared to be absent since no mannose phenylhydrazone could be isolated after treatment of a portion of the non-crystalline syrup with phenylhydrazine solution. The remaining sugar was not identified but may have been *d*-xylose. The above figures show that hydrolysis of the barium salt with N-acid produced 29% of *d*-galactose calculated on the weight of the original barium salt.

The barium salt (3.40 g.) remaining after methyl alcoholic extraction was obtained as a white powder, very soluble in water, giving a yellow solution which reduced Fehling's solution vigorously on boiling. 1 G. of barium salt reduced 39 c.c. of 0.1N-iodine; this is equivalent to a molecular weight of 512. The solution showed $[\alpha]_D^{20} +4^\circ$ (c. 1.0 in water) (Found: OMe, 3.0%, but this value is probably not significant). The barium content of the salt was 15.7%, and on oxidation with nitric acid, mucic acid was produced, in amount showing the presence of some 40% of galactose residues (Calc. for the barium salt of an aldobionic acid; Ba, 16.2; galactose residues, 42%).

(d) *Polysaccharide (A)*. This material (22.5 g.) was obtained as a white powder, easily soluble in water giving a brown solution with an acidic reaction to Congo-red. On boiling it with 12% hydrochloric acid, furfuraldehyde (8.1%) and carbon dioxide (equivalent to the presence of 26.0% of uronic anhydride) were evolved. $[\alpha]_D^{20} +24^\circ$ (in water, c. 0.7). The polysaccharide on being heated with nitric acid (*d* 1.2) gave mucic acid equivalent to the presence of some 50% of anhydrogalactose; this figure is low owing to the difficulty experienced in hydrolysing polysaccharide (*A*) completely. The equivalent (by titration with 0.1N-sodium hydroxide) was 640 (Calc. for a repeating unit containing three hexose residues and a uronic acid residue, 662). On titration with alkaline iodine by the method of Bergmann and Machemer, 1 g. of polysaccharide (*A*) required 23 c.c. of 0.1N-iodine.

Polysaccharide (*A*) (1.49 g.) underwent hydrolysis on heating at 90° with N-sulphuric acid (50 c.c.). $[\alpha]_D^{20}$ changed from $+28^\circ$ (initial value) to $+30^\circ$ (3 hrs., constant value). The iodine titre (in c.c. of 0.1N-iodine per g. of polysaccharide) was 23 c.c. (initial value); 47 ($\frac{1}{2}$ hr.); 57 (1 hr.); 73 (2 hrs.); 75 (3 hrs.). The cooled solution was neutralised with barium carbonate, filtered, and evaporated to dryness, and the residue exhaustively extracted with alcohol. Concentration of the extracts gave crystalline *d*-galactose (0.4 g.), m. p. 164° , $[\alpha]_D^{20} +80^\circ$ (c. 1.3 in water). The residual barium salt showed $[\alpha]_D^{20} \pm 0^\circ$ (c. 2.0 in water). On oxidation with nitric acid (*d* 1.2) it gave mucic acid equivalent to the presence of some 50% of anhydrogalactose, and contained 16.3% of barium (Calc. for a barium aldobionate: Ba, 16.2%).

The barium salt of the aldobionic acid from polysaccharide (*A*) underwent further hydrolysis with much decomposition on being heated at 95° with 4N-sulphuric acid for 24 hours. From the solution, after neutralisation with barium carbonate and filtration, *d*-galactose was obtained in crystals, m. p. 163° , $[\alpha]_D^{20} +77^\circ$ (c. 1.1, in water), and as its phenylmethylhydrazone, m. p. 190° . The barium salt of the uronic acid was identified as barium glucuronate (see below). The total percentage yields of *d*-galactose and barium glucuronate isolated were small, but the proof of the presence of these two compounds combined as an aldobionic acid is furnished by a study of the hydrolysis products of the methylated aldobionic acid.

Methyl heptamethyl aldobionate. The barium salt of the aldobionic acid (3.3 g.) was dissolved in water and the barium precipitated as sulphate by the addition of the calculated quantity of 0.1N-sulphuric acid. The solution was filtered, and the filtrate evaporated to a syrup which was simultaneously esterified and converted into the glycoside by boiling with 2% methyl alcoholic hydrogen chloride for 20 hours. This time of esterification was too long, since much hydrolysis to monosaccharides had taken place. The solution was neutralised with silver carbonate, filtered, and evaporated to a syrup which was methylated by means of thallium hydroxide and methyl iodide in the usual manner (for details, see Hirst and Jones, *loc. cit.*). The methylated material was extracted with acetone, the solvent boiled off, and the residual syrup (2.85 g., n_D^{20} 1.4545) distilled in a vacuum giving:

Fraction I (2.0 g.). Mainly monosaccharides, b. p. 130° (bath temp.)/0.001 mm.; n_D^{20} 1.4495.

Fraction II (0.69 g.). Methyl heptamethyl aldobionate, b. p. 180° (bath temp.)/0.001 mm.; n_D^{20} 1.4680; $[\alpha]_D^{20} +40^\circ$ (c. 1.3 in water) (Found: OMe, 51.3; equiv., 470. Calc. for $C_{20}H_{38}O_{12}$: OMe, 53.0%; equiv. 468).

The methyl heptamethyl aldobionate (Fraction II) (0.67 g.) was hydrolysed by boiling it with 2N-hydrochloric acid (50 c.c.) for 10 hours. The rotation ($[\alpha]_D^{20}$) rose from $+40^\circ$ to $+46^\circ$ in 3 hours, after which the solution became too dark for polarimetric observation. The cooled solution was neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. The solution was then neutralised with barium carbonate and filtered, and the filtrate evaporated to a syrup which was exhaustively extracted with ether. The extracts on concentration gave a syrup (0.27 g.; $[\alpha]_D^{20} +65^\circ$ (c. 1.97 in water); OMe, 41%) which was mainly 2:3:4-trimethyl *d*-galactose, since after heating a portion of it with alcoholic aniline, the characteristic 2:3:4-trimethyl *d*-galactose anilide, m. p. and mixed m. p. 169° , was isolated. The rotation of the isolated sugar is low, probably because of contamination with a little 2:3:5-trimethyl *d*-galactose due to methyl furanoside formation on boiling the aldobionic acid with methyl alcoholic hydrogen chloride (cf. Challinor, Haworth, and Hirst, *loc. cit.*). The

sugar on oxidation with bromine water gave a lactone, $[\alpha]_D^{20} +95^\circ$ in water (initial value), which with liquid ammonia gave 2 : 3 : 4-trimethyl *d*-galactonamide, m. p. and mixed m. p. 165°.

The barium salt remaining after ether extraction was dissolved in water and barium removed as sulphate. The trimethyl *d*-glucuronic acid remaining in solution was oxidised with bromine water and the 2 : 3 : 4-trimethyl *d*-saccharic acid isolated in the usual manner and esterified with methyl alcoholic hydrogen chloride, and the dimethyl ester distilled in a vacuum; b. p. 120° (bath temp.)/0.01 mm. The distillate crystallised on standing. After separation on a tile, the methyl ester of 2 : 3 : 4-trimethyl *d*-saccharolactone was obtained, m. p. 110° not depressed on admixture with an authentic sample. This aldobionic acid was therefore *d*-glucuronosido-1 : 6-*d*-galactose.

Oxidation of the Gum with Potassium Periodate.—(a) The neutral gum (0.25 g.) was dissolved in water (250 c.c.) containing potassium chloride (1 g.) and sodium periodate (20 c.c.; 0.3M) and shaken for 10 days at 15°. Portions (10 c.c.) were taken out at intervals, ethylene glycol was added to destroy excess of periodate, and the formic acid was titrated with 0.01N-barium hydroxide [Titre: 0.65 c.c. (24 hrs.); 0.85 c.c. (72 hrs.); 0.9 c.c. (96 hrs.); 0.9 c.c. (192 hrs. constant)].

(b) The gum (1.399 g.) was dissolved in water (250 c.c.) containing potassium chloride (5 g.) and shaken for 8 days at 17° with sodium periodate (50 c.c.; 0.236M). At the end of this time titration showed that periodate equivalent to 125.6 c.c. of 0.1N-arsenite had been used in oxidising the gum.

In a similar experiment the gum (0.504 g.) required for oxidation periodate equivalent to 47.0 c.c. of 0.1N-arsenite. If, as indicated above, the gum contains four mols. of pentose, three mols. of hexose and one mol. of uronic acid per repeating unit of equivalent 1190, these figures show that an average of 1.07 mol. of formic acid is produced and an average of 5.2 mols. of periodate are consumed per repeating unit.

(c) The gum (0.5 g.) was oxidised in the usual manner for 200 hours. The solution was then cooled to 0° and filtered from potassium periodate. Slight excess of a solution of barium chloride was then added, and the precipitated barium iodate and periodate filtered off. The last traces of periodate and iodate were destroyed by bubbling sulphur dioxide through the filtrate which was then concentrated in a vacuum to a dry solid. A furfuraldehyde determination was then carried out in the usual manner.

In a second experiment the gum (0.5 g.) was oxidised as described above and the salts were then removed by dialysis [Found: Furfuraldehyde, 10.0 and 11.6. Calc. (for the loss of two pentose units and one uronic acid unit by periodate oxidation), 10.9; (for the loss of two pentose units only), 14.6%].

Hydrolysis of the oxidised gum. The oxidised gum (2.864 g.; see above for preparation) was hydrolysed by boiling with N-sulphuric acid (50 c.c.) for 48 hours. Since the solution became very dark and since the polysaccharide did not completely dissolve it was not possible to tell when the hydrolysis was completed. Sulphuric acid was precipitated by the addition of barium hydroxide, and the solution, after filtration, was concentrated in a partial vacuum to a solid. This residue was extracted exhaustively with methanol, and the extracts were concentrated under diminished pressure, to a syrup which was made up to 10 c.c. with water.

A galactose estimation on the solution (4 c.c.) gave 387 mg. of phenylmethylhydrazone, m. p. 186°. This is equivalent to approximately 1.5 mols. of galactose (per repeating unit of equiv. 1220) in the oxidised gum.

An arabinose estimation on the solution (2 c.c.) gave *l*-arabinose benzoylhydrazone (20 mg.), m. p. 180° (decomp.), equivalent to 33 mg. of *l*-arabinose, corresponding to 0.5 mol. of *l*-arabinose residues (per repeating unit of equiv. 1200) in the oxidised gum. This value is certainly low owing to the conversion of arabinose into furfuraldehyde during the hydrolysis, and the true figure is probably nearer one mol.

No xylose could be detected (as the dibenzylidene dimethyl acetal, Breddy and Jones, *J.*, 1945, 738).

Estimation of $-\text{CH}_2\text{OH}$ Groups in the Gum. (Method of Lindstedt, *Arkiv Kemi, Min. Geol.*, 1945, 20 A, No. 13.)—The gum (1.65 g.) was suspended in pyridine (30 c.c.) and triphenylmethyl chloride (5 g.) added, and the mixture heated on a water-bath at 100° for 12 hours. The mixture was then poured into cold water (200 c.c.) and the product filtered off and washed with alcohol and ether. The last traces of triphenylmethylcarbinol were removed by exhaustive extraction with alcohol and the product dried in a vacuum (yield 2.46 g.).

This product was shaken with concentrated sulphuric acid (10 c.c.) for 12 hours. The resultant thick black solution was poured into water and the crude triphenylmethylcarbinol filtered off, washed with water and dilute ammonia, and weighed. The weight of pure triphenylmethylcarbinol was then obtained by exhaustive extraction from the filtered solid with alcohol (Found: 1.05 g. A polysaccharide containing four primary alcohol groups per repeating unit of 1220 requires 1.04 g.).

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[Received, October, 29th 1946.]

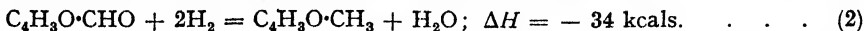
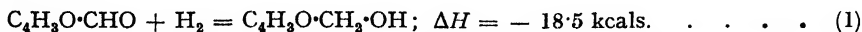
202. The Hydrogenation of Furfuraldehyde to Furfuryl Alcohol and Sylvan (2-Methylfuran).

By JOHN G. M. BREMNER and RICHARD K. F. KEEYS.

Both sylvan and furfuryl alcohol are formed in the hydrogenation of furfuraldehyde in the vapour phase at atmospheric pressure with a copper catalyst. The alcohol is formed in the lower temperature range ($\leq 200^\circ$) and sylvan at intermediate temperatures ($\sim 250^\circ$). At higher temperatures ($\geq 300^\circ$) furfuryl alcohol tends once more to be the main product, but operation under these conditions leads to a rapid decline in catalyst activity. A regular change from the predominance of sylvan to that of furfuryl alcohol occurs with an increase in the amount of

alkali added to the catalyst. The presence of chromium oxides, on the other hand, favours the formation of sylvan. A theory of hydrogenation is proposed to account for these effects.

THE hydrogenation of furfuraldehyde in the vapour phase at atmospheric pressure is reported to give sylvan (2-methylfuran) in excellent yield (Burnette, *Iowa State Coll. J. Sci.*, 1944, 19, 9; Wilson, *J.*, 1945, 61) but other workers find that furfuryl alcohol may be the main product (Ricard and Guinot, F.P. 639,756; U.S.P. 1,739,919; D.R.-P. 528,820; Lazier, U.S.P. 2,077,422). Where this is so, an increased overall conversion of furfuraldehyde into sylvan may be obtained by the further passage of the alcohol over the catalyst or by working at a higher catalyst temperature:



The present work aimed at a more detailed and systematic investigation of the catalytic hydrogenation of furfuraldehyde in the vapour phase. The emphasis was placed on those factors which determine the main product to be furfuryl alcohol or sylvan. The results obtained in this and related work are considered from the standpoint of a theory of catalysis involving the intermediate formation of radicals.

EXPERIMENTAL.

Furfuraldehyde.—The commercial material was distilled at 30–40 mm. The colourless distillate had d_{20}^{20} 1.160, n_D^{20} 1.525, b. p. 161–162°, and contained 0.003% of sulphur.

Hydrogen.—Electrolytic cylinder gas was used containing about 0.001% of carbon monoxide.

Catalysts.—Five different copper catalysts were used.

Copper–aluminium alloy catalysts were prepared from chill castings. The casting was crushed to give $\frac{1}{4}$ – $\frac{1}{2}$ " diameter granules and then activated by treatment with 0.4% aqueous sodium hydroxide at 100°: this removes aluminium from the surface layers but leaves the granule size unchanged (cf. Bag and Egupov, *Uspekhi Khimii*, 1945, 14, No. 1, 56). In these catalysts both the original alloy composition and the amount of aluminium extracted may be varied. The alloys examined contained 34, 55, and 62% of copper and the aluminium extracted varied from 5 to 35%. After activation, the granules were washed with water to remove alkali. The catalyst may be stored under water until required.

Three copper–alumina catalysts were prepared. (A) Cu–Al₂O₃ was prepared by dehydrating alumina trihydrate to the monohydrate, moulding it into $\frac{1}{8}$ " \times $\frac{1}{8}$ " cylinders, and then dehydrating it to γ -Al₂O₃ by heating to 750°. The pellets were impregnated with copper nitrate to give 20% of Cu calculated on Al₂O₃. (B) Cu–Al₂O₃ was prepared by impregnating the commercial activated alumina supplied by the Aluminium Ore Company of America with copper nitrate to give a 20% copper content. (C) Cu–Al₂O₃ was a co-precipitated catalyst formed by addition of sodium carbonate to the mixed metal nitrates. The precipitate, after being washed, was heated to 350°, and then made into cylindrical pellets as above.

A copper chromite catalyst, magnesium promoted, was prepared in similar fashion to that described by Adkins, Connor, and Folkers (*J. Amer. Chem. Soc.*, 1932, 54, 1138). The Cu:Cr:Mg atom ratio in this catalyst was 1:1.05:0.04. The catalyst was used in the form of $\frac{3}{8}$ " \times $\frac{3}{8}$ " pellets.

The copper–alumina and copper–chromite catalysts were reduced by hydrogen before use. Care was taken in this operation not to exceed 400°, the maximum reduction temperature normally being 350°.

The pelleted catalysts may be modified by impregnation with soluble salts. This is readily accomplished by adding to the pellets a volume of aqueous solution such that complete absorption occurs.

Apparatus.—Experiments were carried out in a continuous manner by passage of furfuraldehyde vapour and hydrogen downwards through the catalyst mass. Two types of apparatus were used, in both of which the catalyst tube was vertical. In one, the catalyst, supported on silica granules, was contained in a "Pyrex" glass tube (42" \times 1½") (Fig. 1). The space above the catalyst was packed with silica granules, and acted as a vaporising and pre-heating zone. The temperature through the contact material was measured by a movable iron–constantan thermocouple held in a glass sheath disposed axially down the tube. The catalyst volume was normally 200 ml. The catalyst tube was surrounded by an iron tube heated by three electrical windings independently controlled. In the absence of a pronounced heat of reaction, this arrangement enables a uniform temperature to be maintained throughout the catalyst mass. This apparatus will subsequently be referred to as the "standard" one.

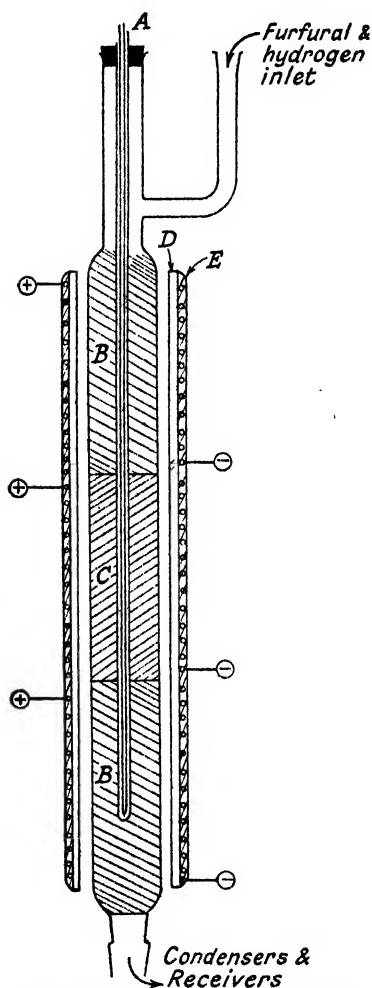
The other apparatus comprised a "Staybrite" metal catalyst tube (45" \times 1") to which was welded a metal jacket (Fig. 2). The catalyst arrangement was as in the glass tube but with the thermocouple sheath of "Staybrite" metal. The jacket was filled with liquid of b. p. suitable to maintain the reaction temperature. The vapour arising from the boiling liquid was condensed and returned. The liquid was heated to the b. p. by electrical windings on the exterior of the jacket. In exothermic reactions the heat evolved is removed by vaporisation of the surrounding liquid. The exterior surface of the catalyst tube is, in this way, held at a constant temperature regardless of the thermal nature of the reaction. This apparatus will subsequently be referred to as the "jacketed" type.

For both catalyst tube arrangements, furfuraldehyde was fed from a calibrated vessel by displacement with hydrogen evolved electrolytically. Hydrogen was admitted to the tube through an integrating rotary gas-meter capable of measuring rates up to about 100 l./hr. The products from the catalyst tube passed through a water-cooled double-surface condenser to a glass receiver. Unreacted hydrogen was passed through two receivers immersed in ice and water and two receivers immersed in solid carbon dioxide–methanol. Material entrained by the gas was recovered in these receivers. The volume of

unreacted hydrogen was measured by an integrating rotary gas-meter. The volume of hydrogen absorbed during the hydrogenation gives an excellent indication of the course of the reaction.

Analysis of Products.—Gaseous products were analysed in an Orsat apparatus. The liquid products were homogeneous if the furfuraldehyde were largely unchanged or if furfuryl alcohol was the main product. With sylvan as the main product, a lower aqueous layer was obtained. Small amounts of aqueous top layer were observed when the product was a mixture of sylvan, furfuryl alcohol, and some

FIG. 1.

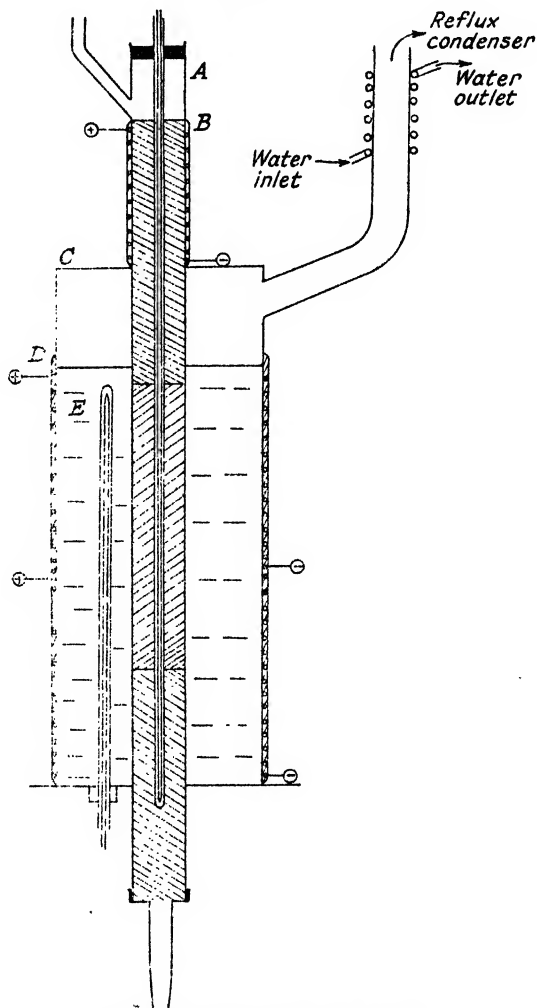


Standard catalyst tube arrangement.

Key to Fig. 1.

- A = Thermocouples.
- B = Silica granules.
- C = Catalyst.
- D = Iron tube.
- E = Electrical windings.

FIG. 2.



Jacketed catalyst tube arrangement.

Key to Fig. 2.

- A = Metal catalyst tube.
- B = Vapouriser.
- C = Metal jacket.
- D = Jacket heaters.
- E = Temperature control liquid.

unreacted aldehyde. In addition to sylvan and furfuryl alcohol, furan and pentanone-2 (Burnette, *loc. cit.*) were sometimes formed in small amount, and a pentanol in traces. Sylvan appears to be the precursor for pentanone-2.* Furfuraldehyde may suitably be estimated in a homogeneous product by titration of the acid liberated on reaction with hydroxylamine hydrochloride. This determination is carried out at room temperature, for, under reflux conditions, furfuryl alcohol also reacts with hydroxyl-

* Sylvan can be hydrogenated in good yield to pentanone-2 by using a copper catalyst (unpublished work).

amine hydrochloride liberating approximately 1 mol. of hydrochloric acid per mol. of alcohol. This effect is presumably due to a ring opening reaction (Pummerer, *Ber.*, 1923, 56, 999). Although both furfuraldehyde (Hughes and Acree, *Ind. Eng. Chem. Anal.*, 1934, 6, 123; *Cereal Chem.*, 1941, 18, 572) and furfuryl alcohol may react with bromine, the use of pyridine sulphate bromide as reagent (Fitelson, *J. Assoc. Off. Agric. Chem.*, 1943, 26, 499; Wilson and Nisbet, *Analyst*, 1946, 71, 183) limits the attack almost completely to furfuryl alcohol. (A fuller description of these analytical methods will shortly be published.)

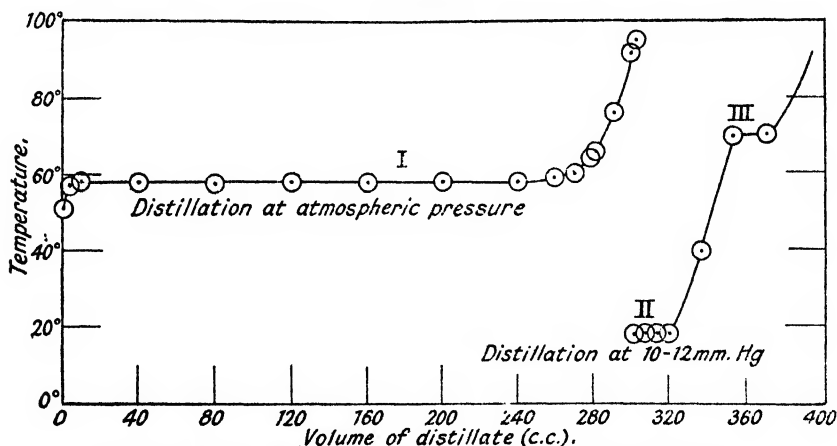
In addition to the chemical analysis of a homogeneous product, both it and the heterogeneous one were fractionated in a column equivalent to about 20 theoretical plates. When 100° was reached, the distillation was continued at about 20 mm. to separate unreacted furfuraldehyde from furfuryl alcohol (Dunlop and Trimble, *Ind. Eng. Chem.*, 1940, 32, 1000). Distillative analysis is not straightforward, for furan, sylvan (Pranishnikov and Genin, *J. Appl. Chem. U.S.S.R.*, 1940, 13, 140), pentanone-2, and furfuraldehyde all form azeotropes with water. As the water content of these azeotropes exceeds the water miscibility at room temperature the distillates separate into two layers (see Table I).

TABLE I.
Water azeotropes: boiling point and composition.

Compound.	B. p.	Water azeotrope.	
		B. p.	Water content (wt. %).
Furan	32°	30.5°	1.2
Sylvan	63	58	4.9
Pentanone-2	102.3	82.9	13.5
Pentanol-2	119.3	92.5	38.5
Furfuraldehyde	162	98	64
Furfuryl alcohol	171	—	—

The low b. p.s of furan and sylvan make their complete recovery during distillation difficult unless cooled condensers and receivers are used. A loss of 5% of sylvan under normal distillation conditions

FIG. 3.



I, Sylvan-water azeotrope; II, Furfuraldehyde-water azeotrope; III, Furfuryl alcohol.

readily occurs. When distilled, furfuraldehyde and furfuryl alcohol tend to polymerise, particularly where impregnated catalysts are used which decompose to give acid vapours on heating. This effect was minimised by addition of sodium carbonate to the receiver in which the liquid products were collected. The results of a typical distillation are given in Fig. 3.

It is clear that where a mixture of products is obtained a rigorous analysis is difficult. When either sylvan or furfuryl alcohol alone is formed the interpretation is greatly simplified.

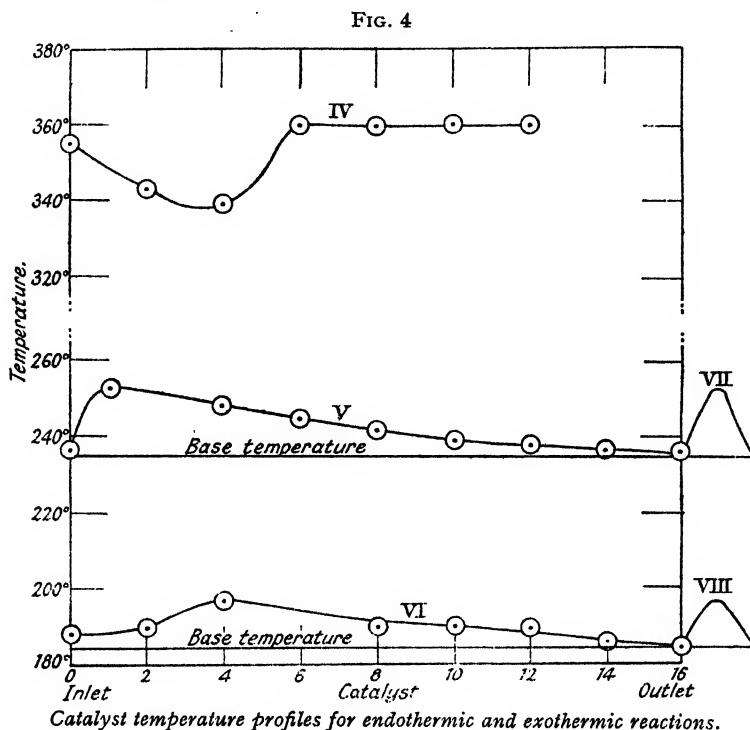
Results.—The terms pass conversion and yield are used to denote, respectively, the percentage of furfuraldehyde used in a single passage over the catalyst and the per cent. of the theoretical yield based on the amount of furfuraldehyde converted. As some 100–150 g. of furfuraldehyde were used in a normal experiment, yields were calculated on the weight and analysis of product obtained so as to counteract the large effect that small weight losses would otherwise have.

The small-scale experiments here described were, in part, the basis for the large-scale preparation of sylvan and furfuryl alcohol. The yields obtained equalled any now given.

Space velocity refers to the volume of furfuraldehyde fed per unit bulk volume of catalyst space per hour.

There is frequently some ambiguity in published work on catalytic reactions as to the interpretation to be placed on the temperature measurements. Normally, only one temperature is given, although it is

evident that the catalyst is not being worked under isothermal conditions. In this work the reaction temperature given is the maximum or peak temperature of the catalyst averaged from recorded half-hourly readings during experiments of a normal duration of 6 hours. In exothermic reactions the catalyst temperature rises rapidly at the beginning of the catalyst mass and then falls off slowly to a steady value which we term the "base" temperature. Typical temperature profiles measured longitudinally down the catalyst mass are given in Fig. 4. Curve VI shows the peak temperature to be only a few degrees above the base temperature for the hydrogenation to furfuryl alcohol ($\Delta H_{298}^0 = -18,500$ cal.). The higher exothermicity accompanying sylvan formation ($\Delta H_{298}^0 = -34,000$ cal.) is evident from curve V,



Longitudinal profiles: IV, Dehydrogenation and dehydration of isopropanol; V, Hydrogenation of furfuraldehyde to sylvan; VI, Hydrogenation of furfuraldehyde to furfuryl alcohol. Radial profiles: VII and VIII, Reactions as for V and VI.

Fig. 4, in which the temperature increment is about 20° . The peak temperature is the important one from the standpoint of reaction rate, while the base temperature controls the pass conversion in those reactions which are reversible under the conditions of the experiment. Reaction (1) is reversible in this sense, but not reaction (2). In addition to the longitudinal temperature profile there is a corresponding radial gradient at right angles. The radial gradient is a maximum at the peak temperature and becomes almost zero in the region of the base temperature. The maximum radial gradients are shown alongside curves VI and V in Fig. 4.

In an endothermic reaction the temperature falls at the beginning of the catalyst mass and rises slowly to the base temperature. This is shown in curve IV, Fig. 4.

DISCUSSION.

(1) *Equilibria in the Conversion of Furfuraldehyde into Furfuryl Alcohol and Sylvan.*—Only the scantiest of thermodynamic data are available for furfuraldehyde and furfuryl alcohol, and none has been published for sylvan. Early work by Landrieu, Bayloq, and Johnson (*Bull. Soc. chim.*, 1929, 45, 36) gives the heat of combustion of liquid furfuraldehyde and furfuryl alcohol. Miller (*Iowa State Coll. J. Sci.*, 1936, 10, 91) gives the free energy of formation of the liquids as -32 and -45.2 kcal., respectively, at 298°K . The latent heat of furfuraldehyde alone has been published (Crawford, *Ind. Eng. Chem.*, 1940, 32, 1280).

For the hydrogenation in the vapour phase of furfuraldehyde to furfuryl alcohol, we derive $\Delta H_{298}^0 = -18.5$ kcal. from the combustion data. In making this calculation we have taken the latent heat of the alcohol to be 1 kcal. greater than that of the aldehyde. From bond energies (Pauling, "The Nature of the Chemical Bond," 1939, Chaps. 2 & 4) we obtain $\Delta H_{291}^0 =$

—17.6 kcal. Both these values are higher than those given for similar reactions (Cubberley and Mueller, *J. Amer. Chem. Soc.*, 1946, **68**, 1149). The resonance energy of sylvan being taken as 24.5 kcal. (Pauling, *J. Amer. Chem. Soc.*, 1939, **61**, 1778), the hydrogenation heat of furfuraldehyde vapour to sylvan is found to be $\Delta H_{291}^0 = -34$ kcal.

The Nernst approximate theorem gives 98 and 60% pass conversion for reaction (1) at 0° and 300°, respectively, but the use of five times the theoretical amount of hydrogen raises the conversion to 96% at 250° at 1 atm.

The Nernst theorem applied to reaction (2) shows conversion to be substantially complete up to 300° at atmospheric pressure even with a stoichiometric ratio of hydrogen.

(2) *The Effect of Catalyst Temperature on the Course of Hydrogenation.*—Experiments carried out with copper-aluminium alloy catalysts (Table II) show the activity of the activated alloy to vary little with composition in the range 34–62% of copper (S.118, S.240, and S.244). The activity is, however, dependent on the amount of aluminium removed during the activation procedure. While it is very small for the original alloy (S.198), the removal of only 5% of aluminium (S.155) gives an active catalyst. Somewhat greater activity is apparent at higher extractions (S.118 and S.162), where, however, the copper surface tends to be removable by abrasion. A convenient extraction is 10–20% and, particularly with the lower value, a catalyst which has become inactive in use may be further extracted to restore the activity. When the activity declines owing to a deposition of carbonaceous material, a high activity results from treatment with air at about 400° followed by reduction with hydrogen (S.126).

The results in Table II show sylvan to be the major product with the alloy catalyst operated in the region of 250° regardless of either the alloy composition or the amount of aluminium extracted. The treatment with air of a catalyst whose activity has declined in use, due to the deposition of carbonaceous material (S.124), leaves unaffected the formation of sylvan in high yield, as does the exposure of the catalyst to air before reaction (S.123). Although these changes in catalyst composition and treatment failed to affect the formation of sylvan, yet experiments conducted at temperatures below about 250° effected a marked change in the products of hydrogenation. At about 200° (S.270) furfuryl alcohol becomes the major product. Whilst this behaviour is not unexpected from previous work, it was surprising to find that at 300° (S.124) the activity of the catalyst declined steadily during operation. Further, this decline in activity was accompanied by an increase in the yield of furfuryl alcohol and a decrease in that of sylvan. The activity of the catalyst could be completely restored by careful treatment with air at a

TABLE II.

*Examination of Cu-Al alloy catalysts.**

Expt. No.	Initial alloy composition, Cu, %.	Al removed, %.	Liquid space velocity (hrs. ⁻¹).	Temp.	Molar ratio, H ₂ /aldehyde.	Duration of expt. (hrs.).	Pass conv. (%).	Yield (%).		Remarks.
								Sylvan.	Furfuryl alcohol.	
S.198	55	Nil	0.22	264°	7.1	1.0	~10	—	—	Al extraction variable.
S.155	55	5	0.16	253	7.3	6.0	90.5	89	2	
S.118	55	20	0.19	248	6.1	6.0	97.6	88	5	
S.162	55	35	0.12	243	6.8	6.25	99	88	3	Alloy composition variable.
S.240	34	20	0.17	254	7.1	5.0	91	89	3	
S.244	62	20	0.15	255	5.8	6.5	99.6	84	6	
S.124	55	20	0.27	300	5.4	6.25	27.6	42	46	Temp. variable.
S.270	55	20	0.18	193	5.7	4.0	63	29	66	
S.123	55	20	0.19	249	4.9	6.25	91.8	87	8	
S.126	55	20	0.17	250	5.3	6.5	98	87	5	Catalyst exposed to air 30 hrs. before experiment.
										Catalyst <i>ex</i> S.124; air-treated at 400°, reduced at 350°.

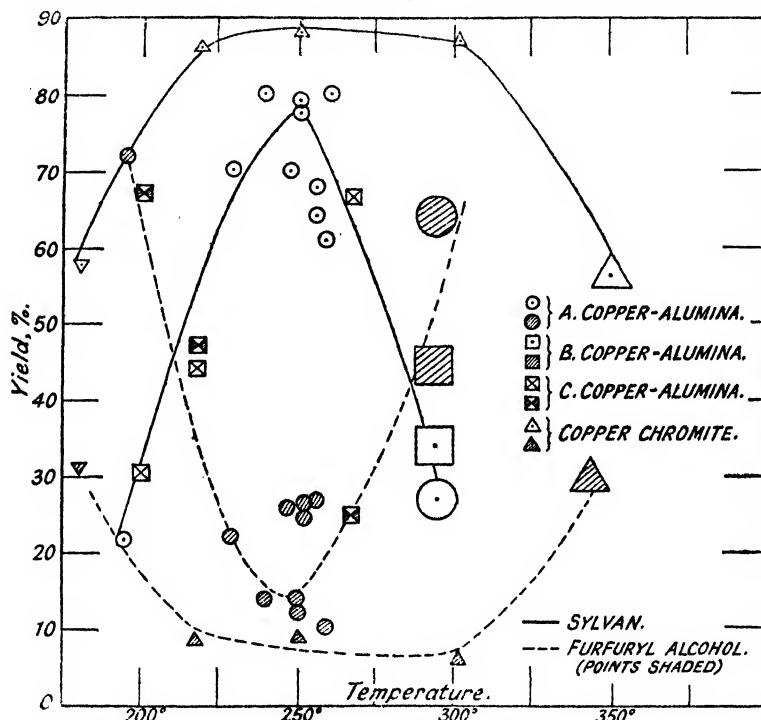
* The standard apparatus was used in all experiments except S.270, for which the jacket apparatus was used.

maximum temperature of about 400°. The peak temperature reached during such treatment is important since the alloy containing 55% of copper melts at 590°. A catalyst which has been worked at such temperatures shows obvious signs of fusion and is rendered permanently inactive.

The effect of temperature on the relative yields of sylvan and furfuryl alcohol was also examined

with the three Cu-Al₂O₃ catalysts A, B, and C. The results are shown graphically in Fig. 5. The hydrogenations were carried out under similar conditions of space velocity and hydrogen : furfuraldehyde ratio to those of Table II. To facilitate the temperature control in the lower range around 200° the jacketed apparatus with decahydronaphthalene (b. p. 190°) as temperature-control liquid was used in these experiments. The results closely resemble those of the alloy catalyst. At around 250° sylvan is formed in high yield, but at 200° furfuryl alcohol is the major product. In the region of 300° fairly rapid catalyst deterioration occurs, and with it a change from sylvan to furfuryl alcohol as the major product. The effect of temperature on pass conversion is shown in Fig. 6. At 200° conversion is not quite complete at a space velocity of 0.27 hr.⁻¹ (S.86) and falls from 80 to 48% (S.101) with an increase in space velocity to 0.66 hr.⁻¹, showing catalyst activity to be the limiting factor. At 250° and the normal space velocity of about 0.2 hr.⁻¹, conversion is practically complete. In the region of 300° the catalyst activity

FIG. 5.



The variations in yield of sylvan and furfuryl alcohol with temperature.

falls away progressively, so the pass conversion depends on the duration of the experiment. Catalysts which have deteriorated in this way may be restored in activity by treatment with air at about 400°, followed by reduction in hydrogen.

The variation in the ratio of sylvan to furfuryl alcohol with temperature is very similar for both the alloy and copper-alumina catalysts. The behaviour of the copper chromite catalyst is qualitatively similar. It is, however, very much less sensitive to temperature variations with regard both to the relative yields of furfuryl alcohol and sylvan and to the onset of deterioration.

The results for this catalyst, given in Table III, show sylvan to be the main product at both 250° and 300°. Even around 200° sylvan is still formed in high yield. A significant increase in the yield of furfuryl alcohol was obtained only by working at even lower temperatures, achieved by substituting furfuraldehyde (b. p. 162°) in the jacket for decahydronaphthalene as temperature-control liquid. In the higher temperature range, the onset of catalyst deterioration with the accompanying formation of furfuryl alcohol occurred only at temperatures near 350°. The results given by the copper chromite catalyst are included in Fig. 5.

(3) *The Effect of Alkalisng the Catalyst on the Ratio of Sylvan to Furfuryl Alcohol.*—At temperatures around 250° different preparations of alkali-precipitated copper catalysts gave sometimes

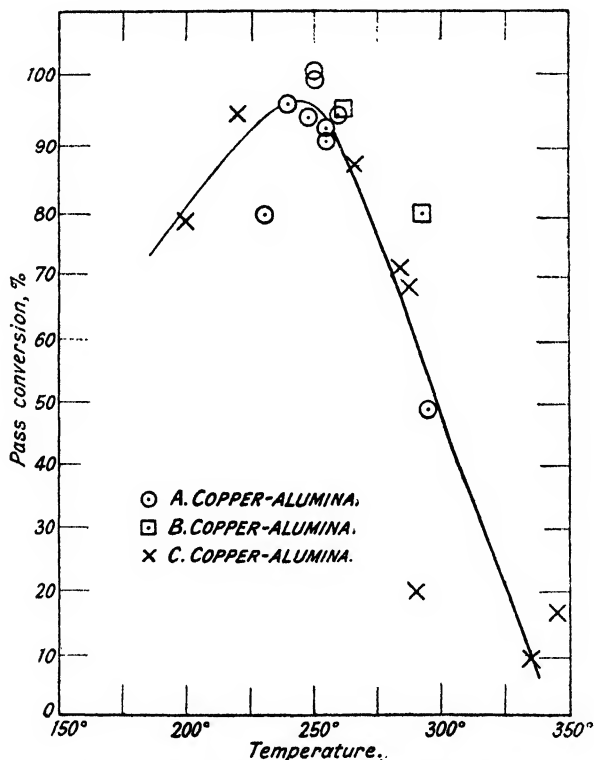
TABLE III.

*Examination of copper chromite catalyst.**

Expt. No.	Liquid space velocity (hr. ⁻¹).	Temp.	Molar ratio H ₂ /aldehyde.	Duration of expt. (hrs.).	Pass conv. (%)	Yield, %.		Remarks.
						Sylvan.	Furfuryl alcohol.	
S.272	0.19	178°	5.8	4.75	97	58	33	Furfuraldehyde as control liquid.
S.267	0.22	217	4.8	5.5	92.7	85	7	Decahydronaphthalene as control.
S.264	0.13	250	7.8	5.5	99	87	7	
S.276	0.13	301	6.2	4.5	98	87	5	
S.277	0.17	346	4.6	5.5	48	55	30	

* Jacketed tube apparatus used in first two experiments, and standard apparatus in last three.

FIG. 6.

*The variation of pass conversion with temperature.*

furfuryl alcohol and sometimes sylvan as the main product. It was considered that this might arise from a variation in the extent of washing of the precipitate, an appreciable amount of alkali being left in the final catalyst in some cases. To test this view, alkali additions were made to a 55% copper alloy catalyst. The results given in Table IV show the presence of alkali markedly to affect the course of the hydrogenation reaction.

Simple immersion of the activated alloy in sodium carbonate solution gave on hydrogenation a mixture of sylvan and furfuryl alcohol, and an almost complete change in the course of the action was achieved only by immersion under reduced pressure, to remove occluded gases. As the amount of alkali added under these conditions is not readily assessed, the A type Cu-Al₂O₃ was modified by successively increasing additions of sodium carbonate. This was accomplished by adding an alkaline solution of the requisite concentration to the pellets of volume such that complete absorption occurred, drying them, and then charging them into the catalyst tube. In this way catalysts containing 0.5, 2.5, 4, and 5% of Na₂CO₃ were prepared and examined at space velocities of about 0.2 hr.⁻¹ and a temperature of about 250°. The results obtained

TABLE IV.

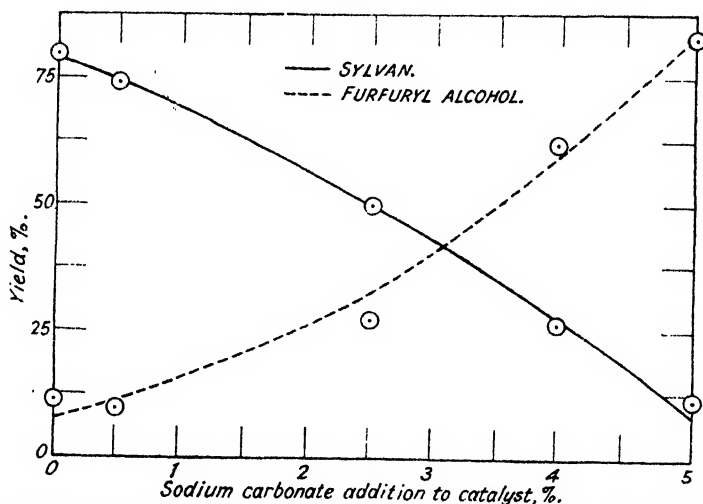
*Alkali addition to a copper alloy catalyst.**

Expt. No.	Liquid space velocity (hr. ⁻¹).	Temp.	Molar ratio H ₂ /aldehyde.	Duration of expt. (hrs.).	Pass conv. (%)	Yield (%).		Alkalisations procedure.
						Sylvan.	Furfuryl alcohol.	
S.185	0.16	253°	7.0	6.5	98.2	88	2	Catalyst only slightly water washed after caustic extraction.
S.186	0.20	254	5.8	6.5	96	32	58	Catalyst immersed in 5% aqueous Na ₂ CO ₃ for 72 hours at room temp.
S.195	0.19	257	4.0	2.5	89	12	70	Catalyst immersed in boiling 5% Na ₂ CO ₃ under reduced pressure.

* Standard type apparatus throughout.

are shown graphically in Fig. 7. Successive additions of alkali change the product from one consisting almost solely of sylvan, to a mixture of sylvan and furfuryl alcohol. At the higher

FIG. 7.



The effect of alkalis on the yields of sylvan and furfuryl alcohol.

alkali additions the alcohol is practically the sole product. That the formation of furfuryl alcohol in this way is due to a high degree of catalyst selectivity was shown by the passage of the alcohol over the catalyst. Sylvan was present in the product to the extent of only 4.8%.

As with temperature variations, the copper chromite catalyst was much less sensitive to alkali addition than the alloy and copper-alumina type catalysts (see Table V).

TABLE V.

*Alkali addition to a copper chromite catalyst.**

Expt. No.	Liquid space velocity (hr. ⁻¹).	Temp.	Molar ratio H ₂ /aldehyde.	Duration of expt. (hr.).	Pass conv. (%)	Yield (%).		Alkalisations.
						Sylvan.	Furfuryl alcohol.	
S.259	0.16	242°	6.9	4.75	98	79	7	5% Na ₂ CO ₃ added to catalyst before pelleting.
S.261	0.16	250	7.0	5.5	98	78	5	5% Na ₂ CO ₃ added by impregnation of pellets.
S.262	0.16	295	6.7	6.0	99	88	3	
S.263	0.15	337	6.9	5.0	61.5	38	45	
S.279	0.18	252	6.5	6.0	99	66	23	20% Na ₂ CO ₃
S.280	0.19	255	5.8	6.0	98	47	44	40% Na ₂ CO ₃ .

* Standard type apparatus.

The addition of 20% sodium carbonate gave some furfuryl alcohol in addition to sylvan. A striking transformation occurred during the experiment (S.280) in which the alkali content was increased to 40%. At the end of half the time projected for the experiment, during which sylvan was formed in excellent yield, a sudden change occurred and a homogeneous product was obtained containing 88.5% of furfuryl alcohol and 4.5% of furfuraldehyde. There is evidently a conditioning period for such a catalyst.

(4) *The Effect of the Presence of Carbon Monoxide in the Hydrogen on the Ratio of Sylvan to Furfuryl Alcohol.*—It was found that the presence of 7.2% of carbon monoxide in the reacting hydrogen left unchanged the formation of sylvan in high yield with a copper alloy catalyst at 250° and of furfuryl alcohol with an alkalisied A type copper-alumina catalyst at 257°. These results are to be considered with the known strong adsorption of carbon monoxide on copper (Pease, *J. Amer. Chem. Soc.*, 1923, 45, 2296) and its prevention at super-atmospheric pressure of the hydrogenation of aldehydes to alcohols in the Roelen reaction (U.S.P. 2,327,066). We conclude that under appropriate conditions both furfuraldehyde and furfuryl alcohol are strongly adsorbed on the catalyst surface.

(5) *Furfuryl Alcohol as Intermediate in the Formation of Sylvan.*—To show that furfuryl alcohol is an intermediate in the formation of sylvan it is necessary to work at incomplete conversion. The previous experiments show the alcohol to be formed in significant amount where conversion is incomplete owing either to a fall in catalyst activity with low operating temperature or to the incidence of catalyst deterioration at higher temperatures. Incomplete conversion may be achieved at the optimum temperature for the formation of sylvan either by using less than the stoichiometric amount of hydrogen or by working at high space velocities. To investigate the former, a copper alloy catalyst was operated at 250° using hydrogen to furfuraldehyde molar ratios of 1.3 and 0.93 (Expt. Nos. S.273 and S.269). The pass conversions were 78% and 32%, respectively. While for the former the sylvan : furfuryl alcohol ratio was 2 : 1, equal amounts of each were formed at the lower conversion.

A pass conversion of 87% was obtained at 258° by working the copper alloy catalyst at the high space velocity of 1.15 hr.⁻¹ (Expt. No. S.281). Under these conditions furfuryl alcohol constituted 26% of the product. This result is similar to that obtained by working with less than the stoichiometric amount of hydrogen (Expt. No. S.273).

The formation of furfuryl alcohol depends on the pass conversion in the manner to be expected of an intermediate product. Furthermore, the passage of the alcohol over the alloy catalyst gave sylvan in 86% yield (S.278).

(6) *Comparison of Furfuraldehyde with Acetone in Ease of Hydrogenolysis.*—Adkins recognises that carbonyl and hydroxymethyl groups are readily reducible to methylene and methyl groups only when attached to an aromatic nucleus (Gilman, "Organic Chemistry," 2nd Edition, I, 804, 820). This conclusion was based, in the main, on work carried out in the liquid phase at super-atmospheric pressure. That it also holds under the experimental conditions used in this work was demonstrated with acetone. Two experiments (S.164 and S.172) in which hydrogen and acetone were passed over a copper alloy catalyst at 249° and 246° gave liquid products which constituted 93.6 and 100% by weight of the acetone fed. *iso*Propanol and acetone dehydration products were present in the liquids. Evidently the extent of hydrogenolysis of acetone to propane is small.

(7) *Analysis of the Products of Hydrogenation of Furfuraldehyde.*—Sylvan and furfuryl alcohol, prepared in the course of this work, were redistilled to give samples for analysis (see

Property.	Material.	
	Sylvan.	Furfuryl alcohol.
d_4^{20}	0.9168	1.129
n_D^{20}	1.4340	1.4846
B. p.	63—64°	—
H ₂ O content, %	0.1	0.43

Table). The unsaturation of the alcohol was measured with the pyridine sulphate-bromine reagent (Found : 304 g. bromine/100 g. Calc. for C₅H₆O₃ : 325 g.).

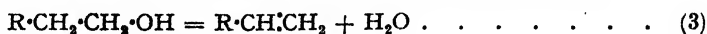
Small amounts of pentanone-2 formed in some of the experiments were bulked together. The once-distilled material had d_4^{20} 0.809; n_D^{20} 1.393. It reacted with hydroxylamine hydrochloride under pressure (Found : CO, 30.0. Calc. for C₅H₁₀O : CO, 32.5%) (Smith and Bryant, *J. Amer. Chem. Soc.*, 1935, 57, 57).

(8) *General Discussion of Results.*—An interpretation of the results obtained in this work must account for the following facts : (a) The ease with which the carbonyl group in furfur-

aldehyde may be reduced to the methylene group. (b) The promotion of the formation of sylvan by chromium oxides and its suppression by the presence of alkali. (c) The probable formation of furfuryl alcohol as intermediate in the formation of sylvan. (d) The formation of furfuryl alcohol in the region of 200° and of sylvan at 250°. (e) The decline in catalyst activity when it is operated at temperatures of 300° or higher.

Observations related to some of those given above have been mentioned in the literature. Reduction of the carbonyl and the nitro-group by chemical means gives products whose nature depends on the acidity or alkalinity of the medium. Acid conditions result in complete removal of oxygen to give methylene and amino-groups. Reduction is less complete under alkaline conditions (Hickinbottom, "Reactions of Organic Compounds," Chaps. IV and VIII), thus qualitatively resembling item (b) above.

In the catalytic field the use of alkalis catalysts has received frequent mention in reactions involving the hydroxyl and the amino-group. Where an alcohol is a product or reactant the former group may be removed by a process of dehydration (3) or hydrogenolysis (4):



The dehydrogenation of alcohols to aldehydes and ketones is accompanied by little olefin formation if alkalis catalysts are used (B.P.P. 313,093, 318,124; U.S.P.P. 1,895,528, 1,984,884). Conversely the yield of alcohol formed by hydrogenation of aldehydes or ketones is not decreased by dehydration if alkali is present (F.P. 671,705; U.S.P. 1,895,515). In addition to suppressing the dehydration of alcohols, addition of alkali can increase the rate of hydrogenation of aldehydes and ketones to alcohols (Delépine and Horeau, *Compt. rend.*, 1935, 201, 1301; Reasenberg, Lieber, and Smith, *J. Amer. Chem. Soc.*, 1939, 61, 384) and of phenols to cyclohexanols (Armstrong and Hilditch, *Proc. Roy. Soc.*, 1922, 102, A, 21; McLaren, "Microfilm Abstracts," University Microfilms, Ann Arbor, 1944, V, No. 2, 39). The hydrogenation of furfuraldehyde in the liquid phase at super-atmospheric pressure is of interest as the presence of alkali causes the reaction to go smoothly in stepwise fashion through furfuryl alcohol to tetrahydrofurfuryl alcohol (U.S.P.P. 1,906,873, 2,082,025; and unpublished work). In the absence of alkali the hydrogenation rate is slow and the by-product formation large.

The addition of alkali to the chromite catalyst used in the hydrogenation of carbon monoxide improves the yield of alcohols higher than methanol (Morgan, Hardy, and Proctor, *J. Soc. Chem. Ind.*, 1932, 51, 1r).

That the loss of a hydroxyl group by the mechanism of equation (4) may also be suppressed by the presence of alkali has been shown by Griffith ("Contact Catalysis," Oxford Univ. Press, 1936, 69) in the case of phenol.

The apparently unrelated observations by Wilson (*J.*, 1945, 55, 61) that the copper chromite catalyst which hydrogenated furfuraldehyde to sylvan in good yield also catalysed the dehydration of tetrahydrofurfuryl alcohol to dihydropyran do, in fact, show the similarity of the two reactions depicted by equations (3) and (4). In demonstrating this similarity we should compare the activity of the catalyst for the dehydration of furfuryl alcohol with its ability to hydrogenolyse this alcohol to sylvan. For simplicity we have, however, examined the behaviour of the catalysts used in this work with isopropanol. The extent of its dehydration to propylene ($\Delta H = 16,200$ cal.) would be expected to be large with those catalysts that favour sylvan formation. The formation of acetone by dehydrogenation ($\Delta H = 13,700$ cal.) is to be expected with those catalysts that favour furfuryl alcohol formation. The results of these experiments carried out at 350° and a space velocity of 10 hr.⁻¹ are given in Table VI. Only 10 c.c. of catalyst were used to give approximately isothermal conditions, and the high space velocity was chosen so as to give incomplete conversion. These conditions tend to minimise effects due to the different activation energies of the dehydration and dehydrogenation reactions. The amounts of acetone and propylene formed are expressed by pass yield, i.e., pass conversion \times yield.

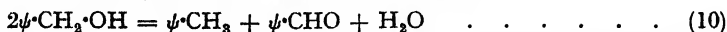
The effect of alkalisation in suppressing the dehydration of isopropanol is evident from the results given in Table VI. The alkalis catalyst, however, shows exceptional behaviour in that it suppresses the dehydration of isopropanol while catalysing the hydrogenolysis of furfuraldehyde. This observation is probably connected with the relative ease of dehydration of isopropanol and furfuryl alcohol, the former occurring the less readily (cf. Storch, *J. Amer. Chem. Soc.*, 1935, 57, 1395).

The use of alkali in the hydrogenation of compounds containing the amino-group includes the hydrogenation of nitrogen to ammonia (Larson and Brooks, *Ind. Eng. Chem.*, 1926, 18,

have a relatively long residence time on the catalyst, during which it will acquire a hydrogen atom to form sylvan.

As is to be expected, hydrogenolysis of tetrahydrofurfuryl alcohol which is much less stabilised by resonance does not, in fact, give tetrahydrosylvan (unpublished work). It seems probable that an appreciable proportion of the hydrogen required for this step is provided by adsorbed furfuryl alcohol molecules as represented by equation (9). A deficiency of hydrogen on a catalyst surface is probable in hydrogenations at atmospheric pressure, more especially where the reaction is carried out in the liquid phase.

The hydrogen atoms of adsorbed alcohol molecules are known to exchange readily (Farkas, *Trans. Faraday Soc.*, 1937, 33, 678). The hydrogen-transfer reaction represented by equation (9) may most simply be regarded as involving a free furfuryl radical formed by the reverse of reaction (5) (Waters, *J.*, 1946, 409; Hey, *Nature*, 1945, 156, 36). That the dehydration of furfuryl alcohol does, in fact, give sylvan and furfuraldehyde by a disproportionation reaction similar to (9) has been shown by Paul (*Bull. Soc. chim.*, 1935, 2, 2220):



Reaction (8) involving an electron transfer is regarded as a rate-determining one. The presence of chromium oxides will confer greater oxidising power or electron-acceptor characteristics to the catalyst and consequently make reaction (8) more likely. Conversely, alkali will increase the electron-donor characteristics of the catalyst and reduce the rate of the carbonium-ion formation. In these circumstances the alcohol formed will tend to be desorbed from the catalyst. The increased rate at which carbonyl compounds are hydrogenated by alkali addition in the liquid phase may be due to the increased catalyst area made available in this way.

The decreased effectiveness of alkali addition with copper chromite catalysts may be accounted for by the counterbalancing action of the chromium oxides. Conversely, we would expect the effects produced by alkalis on a catalyst to be minimised by addition of chromium oxides. This prediction has, in fact, been demonstrated experimentally for the dehydration of ethanol with an alumina catalyst at 350°. The reduction in pass conversion arising from the presence of 2% of sodium carbonate on the alumina is practically eliminated by the subsequent addition of 2% of chromium sesquioxide.

We account for the change in the main product from furfuryl alcohol to sylvan with rise in temperature by the rate-determining nature of reaction (8). The fall in activity observed by operating at even higher temperatures is due to the accumulation on the catalyst surface of non-volatile material of high molecular weight, presumably formed by the interaction of free radicals or ions with the furyl nucleus (Hammett, *op. cit.*, pp. 307, 373; Hey, *loc. cit.*). Such condensation reactions are particularly evident where stabilisation of the intermediates by resonance is possible. Such an explanation may suitably account for the deterioration in catalyst activity observed by Baljassny during his hydrogenation of acetophenone.

It is hoped to publish an account of the implications of this theory to a wide variety of catalytic reactions.

Some of the work described in this paper has formed the subject of patent applications.

The authors wish to express their appreciation to Dr. K. B. Hutton, Miss M. Allan, Dr. S. Beaumont, Dr. R. R. Coats, and especially Dr. D. G. Jones for their part in the early stages of this work. The preparation and examination of some of the catalysts used was carried out by Dr. P. W. Reynolds, Mr. D. M. Grudgings, and Mr. J. A. Mackenzie. Many helpful discussions on theories of catalytic action were held with Mr. D. A. Dowden.

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[Received, November 11th, 1946.]

203. *The Preparation, Properties, and Chlorination Products of Carbon Diselenide.*

By D. J. G. IVES, R. W. PITTMAN, and W. WARDLAW.

The action of methylene chloride vapour on heated selenium readily provides a good yield of carbon diselenide, which thus becomes accessible in considerable quantities for the first time. The vapour pressure of pure carbon diselenide has been measured over a range of temperatures and its behaviour with various reagents and solvents has been given preliminary study. It reacts vigorously with chlorine, giving a variety of products, of which selenium tetrachloride, *perchloromethylselenol*, *hexachlorodimethyl selenide* and *diselenide* have been isolated and characterised. Attempts to prepare selenocarbonyl chloride have not been successful.

THE only practical method hitherto available for the preparation of carbon diselenide depends on the interaction of hydrogen selenide with carbon tetrachloride in a hot tube (Grimm and Metzger, *Ber.*, 1936, **69**, 1356), but, contrary to the statement of these authors, this has been found to give an exceedingly poor yield of diselenide dissolved in excess of carbon tetrachloride, with which it forms an azeotrope. It has been found that methylene chloride vapour reacts with molten selenium with copious production of carbon diselenide, which has thus been prepared in the pure state in considerable quantities. It possesses interesting physical and chemical properties and presents a number of chemical problems which call for further investigation.

Methylene chloride vapour, carried in a stream of nitrogen, begins to react with molten selenium at 500° and produces carbon diselenide smoothly and rapidly at 550–600°. The deposition of carbon in the reaction zone tends to slow down and eventually stop the reaction, but this can be avoided by arranging for the supply of selenium in small quantities at a time to the reaction system. Copious evolution of hydrogen chloride occurs and some selenium is lost as a red, particulate cloud carried over in the gas stream: this difficulty may be partly obviated by the use of a fractionating column kept at about 200°. In a laboratory apparatus designed to meet these difficulties, the best yield of pure diselenide was 52% of the selenium used, without allowance for the considerable amounts of the element which should be easily recoverable from the reaction residues. In the routine preparation, however, a simpler apparatus giving a rather lower yield was found to be advantageous. Attempts to carry out the reaction solely in the vapour phase were unsuccessful, and the impression was gained that it occurs on the surface of liquid selenium.

Other hot-tube experiments of similar type gave no significant results. Methylene chloride gave no carbon disulphide with sulphur at 420°: carbonisation occurred and small amounts of hydrogen sulphide and hydrogen chloride were produced. No carbon sulphoselenide was formed by the interaction of methylene chloride with a mixture of selenium and ferrous sulphide at 425–560°, or by the action of methylene chloride and sulphur vapours on selenium at 500°: small amounts of carbon diselenide were produced in each case. Carbon ditelluride was not produced by the action of methylene chloride on tellurium at 450–680°. Methyl chloride with selenium at 400–550°, in addition to hydrogen selenide and hydrogen chloride, gave traces of a foul-smelling, lachrymatory, yellow liquid, which appeared to be different from carbon diselenide, but was not obtained in amount sufficient for characterisation.

Crude carbon diselenide was readily purified by distillation in steam, followed by distillation under either atmospheric or reduced pressure. It is a bright yellow, non-inflammable, highly refractive liquid (Grimm and Metzger, *loc. cit.*, report n_D^{20} 1.845) which does not wet glass. It has an intolerable odour, causes nose and lung irritation and lachrymation, and has a slight irritant action on the skin. On standing, it darkens, becoming brown, then black and deposits dark polymerisation products: loss of material due to this amounts to about 1% per month. The following physical properties were determined, values in parentheses being those previously recorded by Grimm and Metzger (*loc. cit.*): b. p. 125–126°/760 mm. (124°/760 mm.), m. p. (pentane thermometer) –40° to –45° (–45.5°), d_4^{20} 2.6824 (2.679), d_4^{25} 2.6626. Vapour pressures of the pure diselenide were determined, using a "spoon gauge" incorporated in a high-vacuum apparatus, care being taken to ensure the complete "outgassing" of the sample used and to avoid any possibility of decomposition of vapour during the usual sealing-off procedure. Manometric readings were corrected to 0°, sea-level, and latitude 45°. The results are shown in the table, together with vapour pressures calculated from the equation $\log_{10} P$ (mm.) = 7.9153 – 1987.4/ T , where T is the absolute temperature.

Temp.....	0.00°	5.07°	10.07°	15.07°	20.07°	25.06°	30.04°	35.04°	40.02°	50.01°
$P_{\text{obs.}}$, mm.	4.7	5.7	7.7	10.4	13.6	17.9	23.3	29.6	37.0	58.2
$P_{\text{calc.}}$, mm.	4.4	5.9	7.9	10.4	13.7	17.8	22.9	29.3	37.1	58.3

It will be seen that the vapour-pressure equation fits the experimental points with a mean deviation of ± 0.2 mm. and leads to an average latent heat of evaporation over this temperature range of 9092 cal./mole. Comparison with carbon disulphide has been made by Othmer's method (*Ind. Eng. Chem.*, 1940, **32**, 841), leading to an approximate latent heat of evaporation at the b. p. of 7855 cal./mole and an entropy of evaporation of 19.7 cal./deg./mole. Hildebrand's constant has been calculated as 28.5 (cf. carbon disulphide, 27.1).

Various observations have been made of the behaviour of carbon diselenide with solvents and reagents, in addition to those already recorded by Grimm and Metzger (*loc. cit.*). It is completely miscible with carbon tetrachloride, with which it forms a constant-boiling mixture

containing about 40% of the latter; it is also miscible in all proportions with carbon disulphide and toluene. These solvents appear to retard the polymerisation of the selenide. It is readily soluble in light petroleum (b. p. 60—80°), but in this case the polymerisation does not appear to be retarded. Medicinal paraffin dissolves carbon diselenide to about 25% by volume and the components show an upper critical solution temperature. The diselenide is very sparingly soluble in glacial acetic acid and also in ethanol, which appears to promote decomposition. It is insoluble in water and appears to suffer loss of stability under moist conditions: the upper aqueous layer rapidly becomes turbid. White phosphorus dissolves to a very large extent. Selenium oxychloride reacts violently with carbon diselenide, much elementary selenium being deposited with liberation of unidentified volatile products. Selenium monochloride reacts briskly after a period of induction, giving selenium and a volatile product of intolerable odour. Bromine reacts with a "quenching" sound, giving a clear red liquid which deposits a dark brown solid on standing. Dry hydrogen chloride has no apparent reaction and neither has the concentrated aqueous acid, from which the diselenide steam-distills on boiling. Concentrated nitric acid has little action in the cold, but destroys the diselenide on boiling, although the compound distills in the vapour of the boiling acid for a considerable time. Concentrated sulphuric acid has a more rapid action, but again unchanged selenide can be distilled from admixture for some time. Oleum produces rapid decomposition. Concentrated aqueous sodium hydroxide has little action in the cold, but dissolves carbon diselenide on heating, giving an orange solution. Alcoholic potash dissolves and destroys the diselenide rapidly and affords the best means of decontaminating apparatus which has contained it. Dry bleaching powder produces a vigorous exothermic reaction accompanied by the evolution of most aggressive vapours. It is apparent that there is a wide field of investigation still open in the chemistry of carbon diselenide, but the only reaction which opportunity has allowed us to study is that with chlorine.

Chlorine is absorbed rapidly in large amounts by carbon diselenide, with evolution of much heat. A great variety of interesting products appears to be formed: bright red and yellow solids, white red and black sublimates, red, yellow, and green liquids. Some of these are very unstable; a yellow solid deliquescing rapidly in air, with evolution of pink fumes, provides a striking example. Simplification of this complex reaction was achieved by carrying out chlorination in carbon tetrachloride, in which selenium tetrachloride is sparingly soluble, removal of the latter product by filtration, removal of carbon tetrachloride by distillation, rapid washing of the residue with water, and high-vacuum distillation. Four products were thus characterised with reasonable certainty, the chief of which was selenium tetrachloride. The others were *perchloromethylselenol*, $\text{CCl}_3\cdot\text{SeCl}$, a deep red liquid, b. p. 62°/23 mm., with a biting odour, fuming in air and hydrolysing fairly rapidly with water. *Hexachlorodimethyl selenide*, $(\text{CCl}_3)_2\text{Se}$, was obtained in small amount. It is a white, crystalline solid, m. p. 37°, with an odour resembling that of hexachloroethane. It is soluble in benzene and carbon tetrachloride, and is intermediate in volatility between the above selenol and *hexachlorodimethyl diselenide*, which was obtained in very small yield as a yellow oil, b. p. 126°/0.5 mm., with a camphoraceous odour and an irritant action on the skin. Further treatment with chlorine appears to convert the diselenide into the selenol and selenium tetrachloride.

It is remarkable that no success was achieved in obtaining selenocarbonyl chloride as a product of this chlorination reaction, and although high volatility would not be expected in this compound, it is noteworthy that a volatile selenium compound with a most aggressive and quite intolerable odour has been produced in a number of ways which might conceivably lead to this compound. Such a substance was present in the carbon tetrachloride distilled from the carbon diselenide chlorination mixture, was produced by the interaction of selenium monochloride with carbon diselenide and by the reaction of the latter with dry bleaching powder, and also by the reduction of perchloromethylselenol with anhydrous stannous chloride in carbon tetrachloride solution. The chlorination of selenoformaldehyde was also attempted as a source of selenocarbonyl chloride, but other products, not yet investigated, were produced in this reaction.

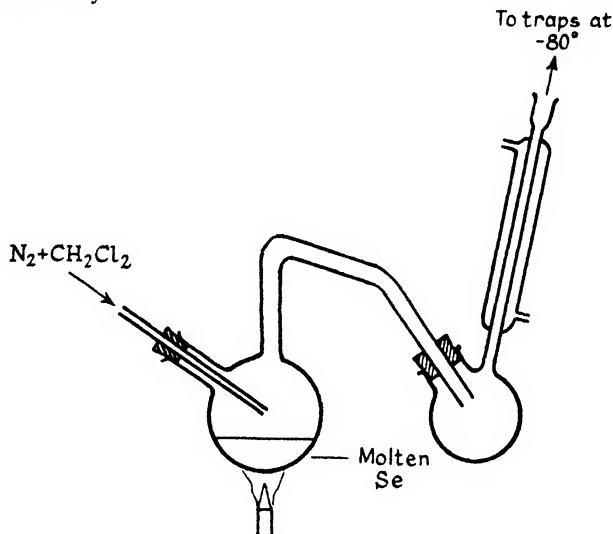
It is clear that much work remains to be done in this interesting field of selenium chemistry, but it is attended by the disadvantage of the rather toxic and highly disgusting nature of the products obtained.

EXPERIMENTAL.

Carbon Diselenide.—Various experimental conditions and types of apparatus indicated the desirability of removing the reaction products as rapidly as possible from the zone of reaction between methylene chloride and molten selenium in order to minimise the deposition of carbon. Too high a temperature

and too extensive a heated zone were also to be avoided from this point of view. These requirements, and the desirability of a reasonable production rate, made unavoidable the loss of considerable amounts of selenium in the form of red smoke, which could ultimately, however, be recovered. The simplest satisfactory apparatus consisted of a Pyrex retort, delivering into a receiver, as indicated in the figure. Methylene chloride vapour, provided by a vessel containing the liquid maintained at a suitable fixed temperature, was delivered above the surface of molten selenium in a stream of dry nitrogen. The crude product was steam-distilled directly from the receiver, separated from the aqueous layer, dried (CaCl_2), and, for purposes of the physical measurements, fractionated through a 30-cm. vacuum-jacketed Dufton column under reduced pressure (b. p. $46^\circ/50$ mm.) (Found: Se, by combustion, 92.77; by Kjeldahl, 92.96. Calc. for CSe_2 : Se, 92.93%).

Chlorination of Carbon Diselenide.—Preliminary attempts at separation of the products of reaction indicated the importance of analyses for selenium and chlorine at frequent intervals. The most rapid and satisfactory methods were found to be as follows: for selenium, digestion with oleum and perhydrol (Kjeldahl), followed by dilution, reduction with sulphur dioxide and then with hydroxylamine hydrochloride, and gravimetric estimation as elementary selenium; for chlorine, treatment with sodium in liquid ammonia, followed, after evaporation of ammonia, by treatment with alcohol, boiling with dilute sulphuric acid, treatment with sulphur dioxide, further boiling, filtration, and precipitation with silver nitrate in the usual way.



The course of a chlorination experiment was as follows. Carbon diselenide (50 g.), dissolved in carbon tetrachloride (300 c.c.) in a 1-l. flask fitted with a mechanical stirrer and reflux condenser, was treated with dry chlorine until an increase in weight of 81 g. was reached (approx. 4 moles of Cl_2). A large precipitate of whitish solid was produced, together with red and yellow sublimes. The reaction mixture was set aside for two days, and darkening occurred. The solid was removed by filtration, washed at the pump with carbon tetrachloride, and proved to be selenium tetrachloride (Found: Se, 35.9; Cl, 64.0. Calc. for SeCl_4 : Se, 35.8; Cl, 64.2%). The filtrate was carefully fractionated, a vacuum-jacketed Dufton column being used with controlled reflux-ratio head. The first distillate, consisting mainly of carbon tetrachloride, was yellow-brown, contained considerable amounts of selenium, and had an intolerable odour reminiscent of carbonyl chloride, but no definite compound could be isolated from it. The residue from this fraction was completely distilled at 200 mm. The second distillate was shaken with water, separated, dried (CaCl_2), and redistilled in vacuum. The first fraction consisted of *perchloromethylselenol* (17 g.), b. p. $62^\circ/23$ mm. (Found: Se, 33.75; Cl, 60.7; *M*, cryoscopic, in C_6H_6 , 247. CCl_3SeCl requires Se, 33.9; Cl, 60.9%; *M*, 233). Further distillation yielded a pale yellow oil which solidified in the condenser. This and the residue in the distillation flask were removed and examined separately. The liquid residue was removed to a smaller apparatus and redistilled (b. p. $124\text{--}129^\circ/2$ mm.). Admission of air to the apparatus caused oxidation, with production of green and red substances. In view of this difficulty and the low volatility of the substance, redistillation was effected in a high vacuum. A small homogeneous fraction consisting of *hexachlorodimethyl diselenide* was obtained (Found: Se, 40.2; Cl, 53.8; *M*, cryoscopic in C_6H_6 , 392. $\text{C}_2\text{Cl}_6\text{Se}_2$ requires Se, 40.0; Cl, 53.9%; *M*, 395). The solid condensate from the previous distillation was recovered by dissolving in carbon tetrachloride. The solvent was removed, and the residue sublimed in a high vacuum, giving a small yield of *hexachlorodimethyl selenide* (Found: Se, 25.3; Cl, 67.4; *M*, cryoscopic in C_6H_6 , 317. $\text{C}_2\text{Cl}_6\text{Se}$ requires Se, 25.0; Cl, 67.4%; *M*, 316).

The authors are indebted to the Director General of Scientific Research (Defence), Ministry of Supply for permission to publish this work.

204. The Relation of Yttrium to the Lanthanons: A Study of Molecular Volumes.

By JOSEPH K. MARSH.

When yttrium concentrates near samarium or neodymium in the lanthanon series, molecular and not ionic states are believed to be involved. The molecular volume of yttrium acetylacetone is found to approximate to that of neodymium, and to be larger than those of the lanthanons similar to yttrium in ionic size. Nevertheless, yttrium basic nitrate and ferricyanide were found to give molecular volumes indicating a polar crystalline state, though they accumulate at the position of No. 61 on fractionation. The basic nitrate will be un-ionised in nitrate solution, and triply ionised ferricyanide is unlikely to reach the solubility product with Y^{+++} or Ln^{+++} . The reaction to form these ferricyanides is therefore believed to be molecular in character, thus accounting for the behaviour of yttrium. This reasoning can be extended to other slightly soluble yttrium salts with multivalent anions (e.g., phosphate, chromate, and ferrocyanide) showing similar behaviour.

IN a previous communication (Marsh, this vol., p. 118) the suggestion was made that yttrium on passing from the ionic to the covalent state underwent a relatively larger increase in size on comparison with the lanthanon elements. For instance, yttrium and holmium ions are approximately of the same size, but sometimes yttrium shows behaviour indicating a resemblance to neodymium and samarium, which elements have larger ions than holmium. Certain sparingly soluble and basic salts incline to show yttrium associating with elements larger than holmium. A reason for this behaviour is now sought.

It is firmly established that a progressive fall in ionic radius with increasing atomic number occurs between lanthanum and lutecium. This is found by X-ray determination of the crystal-lattice size, and is confirmed by determination of the molecular volumes of the sulphate octahydrates (von Hevesy, *Z. anorg. Chem.*, 1925, **147**, 217; **150**, 68), though in both these instances the first two or three members of the rare-earth group lack isomorphism with the remainder. In the oxide series the yttrium ion falls in size between those of dysprosium and holmium, and in the sulphate series between holmium and erbium ions. The latter is the position usually taken by yttrium in a fractional crystallisation series, indicating an important correlation between ionic and molecular sizes and chemical properties in the lanthanon series. Generally, yttrium is isomorphous with holmium and erbium, but exceptions are known. For example, the 2-bromo-5-nitrobenzenesulphonates of yttrium crystallise with $10H_2O$ similarly to those of samarium and gadolinium and in contrast to the dodecahydrates of erbium and ytterbium. Direct evidence of yttrium having at times a larger volume than holmium is now sought by measurement of molecular volumes: it has already been reported in the case of the atomic volumes of the metals (Bommer and Hohmann, *Z. anorg. Chem.*, 1939, **241**, 268). The crystalline basic nitrates and the ferricyanides have been examined throughout a representative series of earths. These are two good examples of salts by the formation of which rapid accumulation of yttrium with neodymium and samarium, and separation from the "yttrium earths", is brought about, but in both instances the molecular volume of the yttrium salt proved to have a value which placed yttrium in sequence in the usual ionic position among the other elements, i.e., near to holmium. The crystals must therefore be regarded as polar in type. The acetylacetones, however, gave evidence that this covalent yttrium compound has in fact a larger molecular volume than that of the usual associates of yttrium in its ionic state.

The basic nitrates are obtained by crystallisation from hot concentrated nitrate solutions. They are decomposed by water, but in nitrate solution they appear to be stabilised by suppression of ionisation by a common-ion effect, on removal of which they hydrolyse. They may be regarded as existing in a non-ionising solvent only. If, then, they exist in solution in a non-ionised form, it is not surprising to find that the solubility of yttrium basic nitrate has a value interpolating in the lanthanon series at the position of No. 61, the same as is found in the case of the atomic volume, or the acetylacetone molecular volume. We must then postulate a transition from a non-ionic to an ionic state upon crystallisation, based on the evidence of the crystal molecular volumes. The precipitate produced by boiling a nitrate solution with sodium nitrite, being chiefly the basic nitrate $Y_8O_{14}(NO_3)_4 \cdot 17H_2O$ (Fogg and James, *J. Amer. Chem. Soc.*, 1922, **44**, 397), appears to be a similar case to the basic nitrate $Y_6O_8(NO_3)_6 \cdot 20H_2O$ produced by crystallisation (James and Pratt, *ibid.*, 1910, **32**, 873).

In the case of the ferricyanides, high concentrations of potassium ferricyanide and up to 200 g./l. of yttrium oxide in the form of chloride can be brought together in cold solution without any precipitate forming, yet the solubility of $YFe(CN)_6$ at 20° is represented by only

0.602 g./l. of Y_2O_3 (Prandtl and Mohr, *Z. anorg. Chem.*, 1938, **236**, 243). Seeding is ineffective in producing a precipitate. Indeed, the seed may dissolve, but on gentle warming a precipitate forms slowly, which has a molecular volume indicative of an ionic state of yttrium. An irreversible reaction takes place, since the precipitate will not redissolve appreciably on cooling. The formation of yttrium ferricyanide according to the simple equation $Y^{+++} + 3Cl^- + 3K^+ + Fe(CN)_6^{---} = YFe(CN)_6 + 3KCl$ cannot be expected to take place, since triple ionisation of ferricyanic acid is necessitated. Thus, in general, it will be seen that molecular reactions may be expected where the alternative involves the existence of a multivalent anion or the production of a series of unknown intermediates. Ferrocyanide, chromate, and phosphate are other examples of salts of yttrium showing closer resemblance to neodymium than to holmium in fractionations. All are compounds having low solubilities and are salts of multivalent acids incapable of complete ionisation.

A series of acetate molecular volumes have been measured, and as anticipated yttrium takes an ionic position in the series. The densities and molecular volumes of the four series of salts examined are presented in Table I. The values for the acetylacetonates might be doubled, since the molecules are known to be double in solution. No high degree of accuracy for the molecular volume determinations can be claimed for these last compounds, but the results are sufficiently reliable to prove the point that the value for yttrium does not lie in the sequence close to those of the other yttrium earths, but is larger and more nearly equal to that of neodymium. The fused acetylacetonate compounds were usually somewhat basic as indicated by high oxide contents on ignition. The densities found must therefore tend to be high and the molecular volumes low. For Table I, data have been selected from the italicised data of Table II,

TABLE I.

Densities.

	La.	Nd.	Sm.	Gd.	Dy.	Y.	Er.	Yb.
Acetates	—	1.885	1.942	1.990	2.042	1.689	2.075	2.142
Basic nitrates	—	—	2.940	3.045	3.159	2.431	3.223	3.326
Ferricyanides	2.044	2.110	2.179	2.243	—	1.937	2.348	2.410
Acetylacetonates	1.542	1.618	1.651	1.678	1.709	1.403	—	1.748

Molecular volumes.

Acetates	—	208.7	205.8	205.0	201.6	200.4	199.9	197.1
Basic nitrates	—	—	634	617	605	605	602	594
Ferricyanides	207	203	199	197	—	193	192	190
Acetylacetonates	283	273	271	271	269	275	—	269

TABLE II.

Acetylacetonates.

	Density.			Oxide, %.			Calc.	Molecular volume.			Best.	Oxide, % in excess.
	1.	2.	3.	1.	2.	3.		1.	2.	3.		
La ...	1.536	1.549	—	36.75	35.82	—	37.34	284.0	281.6	—	283	—2.9
Nd ...	1.618	1.664	1.694	39.05	40.80	41.34	38.11	273.3	265.4	260.5	273	2.5
Sm ...	1.636	1.666	1.689	40.92	40.43	42.22	38.95	273.7	268.8	265.1	271	5.6
Gd ...	1.676	1.712	—	42.33	43.62	—	39.82	270.7	265.4	—	271	6.3
Dy ...	1.709	1.726	—	42.94	45.25	—	40.55	269.1	266.5	—	269	5.9
Y ...	1.393	1.400	1.416	30.83	29.85	31.47	29.23	277.1	275.2	272.7	275	5.1
Yb ...	1.740	1.746	1.759	43.58	43.60	41.28	41.90	270.5	269.5	267.5	269	2.2

sometimes by averaging, but more often by selection of the value relating to the acetylacetonate sample which showed the nearest approach to theoretical oxide content. A fairly constant density increment of 0.03 between even-numbered elements from neodymium to dysprosium inclusive is found, and the excess oxide, except in the case of neodymium but with the addition of yttrium, is also fairly constant, so that this sequence of elements is comparable, and they lend mutual support. It was found that lanthanum acetylacetonate was slightly volatile. Its true oxide content cannot therefore be determined by ignition and the low contents recorded in Table II are suspect. On the other hand, the low densities for the acetylacetonate leading to an unexpectedly high value for the molecular volume are consistent with the presence of excess acetylacetonate, but the melts were not gummy, as would be expected in that event, but quite vitreous. This in other instances accompanied deficient acetylacetonate.

If we examine the molecular volumes of isomorphous compounds of neodymium and ytterbium, we find the values for the latter smaller than those of the former by the following percentages: sulphates 7.0, ferricyanides 6.5, acetates 5.6, ethyl sulphates 3.0. The fall in the case of the acetylacetone compounds appears to be under 2%.

EXPERIMENTAL.

Densities.—In the case of the acetates, suspension of crystals in mixtures of chloroform and bromoform and determination of the density of the liquid by a Westphal balance proved very satisfactory. With basic nitrates and ferricyanides, determinations of the loss of weight in chloroform was more satisfactory, and the acetylacetones were weighed in water. A platinum bucket of 2 ml. capacity and about 0.5 g. of substance were used in these three cases. The accuracy of the method depended chiefly on the proper release of air bubbles before weighing in liquid.

Acetates, $E(C_2H_3O_2)_3 \cdot 4H_2O$.—The neodymium salt was prepared by evaporation of a solution in a desiccator. It is rather efflorescent, but large crystals may be grown. The other acetates crystallised readily from warm neutral solutions, and are stable.

Basic Nitrates, $E_2O_5(NO_3)_8 \cdot 20H_2O$ (James and Pratt, *loc. cit.*).—The normal slightly acid nitrates were boiled to dryness and heated till some decomposition had occurred. The vitreous melts were then poured into cold water and gave clear hot solutions which deposited crystals overnight. It was found possible to prepare the samarium basic nitrate if only slight decomposition of the melt was permitted, for its range of stability is small. The melt was vitreous like the others. Neodymium gave no vitreous melt or basic nitrate crystals. The nitrate creamed at once when decomposition began.

The density of the erbium salt as given in Table I is an extrapolation from the experimental value using material containing 2% of yttrium. Only a very small sample of dysprosium basic nitrate was available, and the single determination of the molecular volume appears low. Other values are believed to be correct within ± 2 . Three determinations for yttrium were within 1 part in 500.

Ferricyanides, $EF_6(CN)_6 \cdot 4H_2O$.—Neutral chloride solutions containing 100 g./l. of oxide were treated at 40–50° dropwise with cold saturated potassium ferricyanide with mechanical stirring and the precipitate which formed was collected, washed, and dried. The precipitates of samarium and gadolinium could not be obtained as coarsely crystalline as in the other cases. Prandtl and Mohr (*Z. anorg. Chem.*, 1938, **236**, 243; **237**, 160) found some variation in the amount of water of crystallisation in the different salts but apparently without loss of isomorphism: e.g., for the lanthanum salt they found $4.5H_2O$, but the molecular volumes shown in Table I are calculated for $4H_2O$ in all cases.

Acetylacetone Compounds, $E[CH(CO \cdot CH_3)_2]_3$.—Acetylacetone (3 g. in 10 ml. of alcohol) was added to an equivalent of lanthanum acetate in 50 ml. of cold water, and ammonia added dropwise with stirring, excess being avoided. The acetylacetone compound soon separated and was collected with suction. Especially in the case of ytterbium, acetylacetone washing appeared to decompose the precipitate. Washing was therefore omitted or kept to a minimum, but the products were well pressed on filter-paper and dried in a desiccator. Melting points were found to be close to known values without further purification.

Lanthanum acetylacetone. The precipitate appeared to be basic and did not give a clear melt unless one or two drops of acetylacetone were added before fusion; then clear melts giving a vitreous, pale amber solid were obtained.

Neodymium acetylacetone. This, m. p. 150–152°, like the lanthanum compound, appeared basic (Found: Nd_2O_3 , 39.04. Calc.: Nd_2O_3 , 38.11%) and failed to give a clear melt without additional acetylacetone.

Gadolinium acetylacetone. This compound, m. p. 140°, was likewise basic (Found: Gd_2O_3 , 40.53. Calc.: Gd_2O_3 , 39.83%). Unlike preparations previously reported it did not appear to contain any water of crystallisation (1 and 2 H_2O , Jantsch and Meyer, *Ber.*, 1920, **53**, 1594; 3 H_2O , Sarkar, *Bull. Soc. chim.*, 1926, **39**, 1390). If damp acetylacetones were heated to their m. p. they reacted with water to form the hydroxides and failed to give satisfactory melts.

Ytterbium acetylacetone. This had m. p. 114° but the melt was not clear. It did not gas at the m. p., as occurred with the higher-melting acetylacetones melting near the b. p. of free acetylacetone. It was not considered likely that satisfactory density determinations by weighing the finely crystalline compounds in water could be made, nor could organic liquids be used, since they have solvent action. Quantities of about 1 g. were therefore fused in an oil-bath in thin 10-mm. specimen tubes with, when necessary, the addition of one or two drops of acetylacetone to give clear melts. Loss of acetylacetone occurred at the m. p. Unless a slight loss did occur, the fused mass cooled to a stiff gum which would quickly crystallise if kneaded. But when slightly basic, a vitreous resin was obtained in one or more large pieces on breaking the tubes, and the densities of these pieces could be obtained with a fair degree of accuracy by weighing in water. There was, however, always some devitrification or hydroxide formation on the surface in contact with water, with loss in weight. The surface deposit was removed so far as possible after determining the density, and the percentage of oxide contained in the material was obtained by ignition. In some cases burning the oxide free from carbon was difficult. The char required to be broken down with a glass rod in the silica crucible before final ignition. Particular care was taken to obtain reliable data for yttrium. The three analyses are in satisfactory agreement but the third shows a high density and high oxide content and low molecular volume. The final figure adopted in Table II for the molecular volume of yttrium acetylacetone is therefore likely to be a little low.

Dr. A. S. Russell is thanked for permission to use this laboratory.

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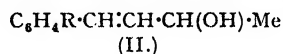
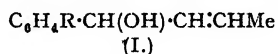
[Received, November 9th, 1946.]

205. *The Preparation and Ultra-violet Light Absorption of Some Substituted Phenylpropenyl- and Styrylmethyl-carbinols and 1-Phenylbutadienes.*

By ERNEST A. BRAUDE, E. R. H. JONES, and E. S. STERN.

In connexion with kinetic studies on anionotropic rearrangements (see following paper), carbinols of the type $C_6H_4R \cdot CH(OH) \cdot CH:CHMe$, where $R = o\text{-Me}, m\text{-Me}, p\text{-Me}, p\text{-F}, p\text{-Cl}, p\text{-Br}$ and $p\text{-MeO}$, have been prepared by Grignard condensations of appropriate aromatic halides with crotonaldehyde. Quantitative conversions into the isomers $C_6H_4R \cdot CH:CH \cdot CH(OH)Me$ are effected by treatment with hydrochloric acid in aqueous dioxan. Dehydration of the carbinols by distillation from potassium hydrogen sulphate yields the dienes $C_6H_4R \cdot CH:CH \cdot CH:CH_2$, which are characterised by their adducts with maleic anhydride and with benzoquinone. The ultra-violet light absorption properties of the various compounds are discussed and provide evidence for the smaller polarisability of the phenyl nucleus as compared with the ethylenic bond.

THE extension of the kinetic studies on anionotropic rearrangements carried out in these laboratories (cf. Braude and Jones, *J.*, 1946, 122, 128; Braude, Jones, and Stern, *ibid.*, p. 396) required the preparation of substituted phenylpropenylcarbinols (I) and of the isomeric styrylmethylcarbinols (II). Only the parent carbinols (I and II, $R = H$) have been described



hitherto. A number of substituted phenylvinylcarbinols have been prepared by Burton and Ingold (*J.*, 1928, 904) and Burton (*ibid.*, p. 1650), but the lower mobility of phenylvinyl- as compared with phenylpropenyl-carbinol (Braude, Jones, and Stern, *loc. cit.*) indicated that the vinylcarbinols would be less valuable for kinetic studies than their propenyl homologues.

The simplest route to phenylpropenylcarbinols is by the Grignard condensation of the appropriate aryl halides with crotonaldehyde. Qualitative data in the literature (cf. Runge in Schmidt, "Chemie in Einzeldarstellungen," Vol. 16, Part I, Stuttgart, 1932) indicate that the reactivity of aryl halides towards magnesium varies in the order $ArCl < ArBr < ArI$. Furthermore, it is said to be enhanced by methyl substituents, decreased by halogen and methoxyl substituents, and completely destroyed by substituents, such as the nitro-group, exerting only electron-attracting effects. The range of compounds accessible by this method is therefore limited. In the present work it was found that the bromotoluenes and *p*-bromofluorobenzene all reacted readily with magnesium in the presence of a small amount of ethyl bromide. *p*-Dibromobenzene and *p*-bromoanisole reacted somewhat less readily, while with *p*-dichlorobenzene the reaction was incomplete even after four days. With *p*-diiodobenzene the metal slowly disappeared after prolonged treatment, but in contrast to the findings of Bruhat and Thomas (*Compt. rend.*, 1926, 183, 297; cf. Mihailescu and Caragea, *Chem. Zentr.*, 1930, I, 2248) no significant yield of condensation product with crotonaldehyde could be obtained, some of the diiodobenzene being recovered unchanged, together with iodobenzene, and intractable residues. Attempts to make *p*-bromonitrobenzene react with magnesium, using Grignard's technique (*Compt. rend.*, 1934, 198, 625) of adding an equimolecular proportion of ethyl bromide simultaneously with the unreactive halide, only yielded unchanged starting material and small amounts of *pp'*-dibromo-azo- and -hydrazo-benzenes (cf. Werigo, *Annalen*, 1873, 165, 190; Hepworth, *J.*, 1920, 117, 1004; Slotta and Heller, *Ber.*, 1930, 63, 3030). Again, the bromomagnesium derivative of *p*-bromophenol, though soluble in anisole at 100°, failed to react with magnesium.

The Grignard derivatives of the first eight halides mentioned were condensed with crotonaldehyde, special attention being paid to temperature control during the addition of the aldehyde and during the decomposition of the complex with ammonium chloride, in order to avoid the formation of the isomeric styryl derivatives. Thus, even in the preparation of the much less readily isomerised phenylvinylcarbinol, the product contains some cinnamyl alcohol unless the last two stages are carried out below 20°. It is known that, *vice versa*, cinnamylmagnesium chloride reacts partly in the form of phenylvinylcarbiniylmagnesium chloride (Gilman and Harris, *J. Amer. Chem. Soc.*, 1927, 49, 1825) and it may well be, therefore, that the Grignard derivatives themselves undergo some equilibration.

The substituted phenylpropenylcarbinols were isolated in good yields as viscous liquids or low-melting solids. In view of their ready isomerisation in the presence of acids, traces of the latter were excluded by drying over, and distilling from traces of, potassium carbonate.

In the absence of these precautions, some of the rearranged styrylmethylcarbinols and phenylbutadienes are invariably produced, and considerable resinification occurs. This is particularly noticeable with the highly mobile *p*-anisylpropenylcarbinol.

Rearrangement of the phenylpropenylcarbinols was effected by treatment with hydrochloric acid in aqueous dioxan, the corresponding styryl isomers being obtained in almost quantitative yields. In aqueous alcohol a mixture of the carbinols and their ethyl ethers is produced (cf. Braude, Jones, and Stern, *loc. cit.*) and kinetic data (see following paper) indicate that with the chloro- and bromo-carbinols some etherification occurs before, as well as during, rearrangement.

Treatment of the phenylpropenylcarbinols with α -naphthyl isocyanate in the absence of solvent gave the naphthylurethanes of the corresponding styrylmethylcarbinols. In petrol solution and in the presence of traces of pyridine, mixtures of the isomerised and unisomerised naphthylurethanes were obtained. The latter could not be isolated pure, however, as they readily rearrange to the former on attempted recrystallisation. The two types of derivatives are distinguished by their characteristic ultra-violet light absorption (see below).

It has long been known that methylstyrylcarbinol can readily be dehydrated to phenylbutadiene (Klages, *Ber.*, 1902, **35**, 2650); in fact, early workers experienced considerable difficulty in obtaining the pure carbinol by the condensation of cinnamaldehyde with methylmagnesium iodide because they omitted to eliminate traces of iodides and of acids which act as dehydration catalysts. In the present work, the rearrangement and subsequent dehydration of the phenylpropenylcarbinols were conveniently carried out in one stage by means of potassium hydrogen sulphate. The carbinol together with about one-tenth of its weight of sulphate is preheated to 80–100° at 10^{-3} mm. until the vigorous rearrangement reaction sets in (5–30 mins.). In the case of the *p*-anisyl- and *p*-bromophenyl-propenylcarbinols the solid styryl isomers are deposited on the sides of the vessel. The temperature is then raised and the phenylbutadiene distils over as the dehydration proceeds. The ease of dehydration appears to vary in the same order as that of the isomerisation of the parent carbinols. The substituted phenylbutadienes are highly refractive liquids or low-melting solids which were purified by micro-fractionation from traces of potassium hydrogen sulphate or by crystallisation, and showed the expected selective high-intensity absorption in the ultra-violet (see below). On heating or on exposure to light and air, they readily resinify, and some difficulty was experienced in obtaining correct microanalyses, particularly for the tolyl compounds.

The dienes were characterised by their reactions with maleic anhydride and with *p*-benzoquinone in benzene solution, giving respectively the phenyltetrahydrophthalic anhydrides and the phenyl-1 : 4 : 9 : 10-tetrahydronaphtha-5 : 8-quinones (cf. Diels and Alder, *Ber.*, 1929, **62**, 2081, 2337). The tetrahydro-quinones are pale yellow owing to their absorption band near 3650 Å. (see below), but slowly change on standing into the colourless phenyl-1 : 4-dihydronaphtha-5 : 8-quinols. This double prototropic change is facilitated by exposure to light, and the ease with which it occurs again appears to parallel that of the isomerisation of the phenylpropenylcarbinols. Thus the *p*-anisyl derivative does not even show the expected light absorption maximum at 3650 Å. in hexane, chloroform, or benzene solution; maxima near 3300 Å. expected for the 1 : 4-dihydronaphthalene derivative (cf. Morton and de Gouveia, *J.*, 1934, 916) appear instead, and only the colourless quinol can be recovered from the solution. Since the last two solvents are not appreciably transparent to light of wave-lengths shorter than 2350 and 3000 Å. respectively at the cell thickness used (1 cm.), the wave-length of the photochemically active light seems to be within the region of the 3650 Å. band expected for the tetrahydronaphthaquinone.

The light absorption properties of the various compounds were determined in the region 2150–4000 Å. In the phenylpropenylcarbinols (Table I), the phenyl and ethylene chromophores are in isolated positions, and would therefore be expected to contribute independently to the ultra-violet light absorption (cf. Braude, *Ann. Reports*, 1945, **42**, 105). The selective absorption of the ethylenic double bond lies well below 2150 Å., and the absorption of the carbinols in the region examined should therefore be closely similar to that of the corresponding substituted toluenes, as is found to be the case.

In the styrylcarbinols (Table II, Figs. 2 and 3), the essential chromophore is the styrene system. Styrene exhibits two bands in the region examined, at 2450 and 2920 Å. (Pestemer, Langer, and Manchen, *Monatsh.*, 1936, **68**, 326), which can be assigned to the conjugated system and to the partial phenyl chromophore respectively. The styrylcarbinols exhibit similar bands, showing small bathochromic displacements of 10–180 Å. due to the substituents, except that a *p*-fluoro-group produces a hypsochromic shift of 30 Å. In the naphthylurethanes

(Table III) the absorption originating in the naphthyl residue is superimposed on the styryl absorption and the difference in the absorption of the naphthylurethanes of the styrylcarbinols and of methanol coincides with the absorption of the styrylcarbinols themselves.

TABLE I.
*Ultra-violet light absorption of $C_6H_4R \cdot CH(OH) \cdot CH \cdot CHMe$ in ethanol.**

R.				R.			
H	$\lambda_{max.}$, A.	—	2510, 2580	<i>p</i> -F	$\lambda_{max.}$, A.	—	2580, 2640, 2700
	$\epsilon_{max.}$	—	450, 450		$\epsilon_{max.}$	—	1450, 1450, 1050
<i>o</i> -Me	$\lambda_{max.}$, A.	2,150	2590, 2640, 2700, 2810	<i>p</i> -Cl	$\lambda_{max.}$, A.	2,220	2590, 2640
	$\epsilon_{max.}$	11,000	480, 510, 400, 130		$\epsilon_{max.}$	11,000	2300, 2300
<i>m</i> -Me	$\lambda_{max.}$, A.	—	2420, 2515, 2580, 2650, 2700, 2725	<i>p</i> -Br	$\lambda_{max.}$, A.	2,230	2590, 2650
	$\epsilon_{max.}$	—	1050, 1150, 1450, 1450, 1150, 1000		$\epsilon_{max.}$	13,000	1500, 1500
<i>p</i> -Me	$\lambda_{max.}$, A.	2,220	2595, 2645, 2720	<i>p</i> -MeO	$\lambda_{max.}$, A.	2,280	2730, 2760, 2815
	$\epsilon_{max.}$	11,000	270, 310, 280		$\epsilon_{max.}$	13,500	2200, 2200, 2100
<i>Ultra-violet light absorption of $R \cdot C_6H_4 \cdot Me$ in ethanol for comparison.</i>							
<i>p</i> -Me	$\lambda_{max.}$, A.	2,160	2600, 2680, 2740	<i>p</i> -MeO	$\lambda_{max.}$, A.	2,240	2800, 2850
	$\epsilon_{max.}$	7,500	330, 500, 620		$\epsilon_{max.}$	10,400	2200, 1530
<i>p</i> -Br	$\lambda_{max.}$, A.	2,200	2620, 2690, 2770				
	$\epsilon_{max.}$	10,500	390, 470, 390				

* In this and subsequent tables figures in italics refer to inflections.

TABLE II.
Ultra-violet light absorption of $C_6H_4R \cdot CH \cdot CH \cdot CH(OH)Me$ in ethanol.

R.				
H	$\lambda_{max.}$, A.	2480, 2510	2810, 2910	
	$\epsilon_{max.}$	19,000, 19,500	2000, 1550	
<i>o</i> -Me	$\lambda_{max.}$, A.	2480, 2550	2880, 2970	
	$\epsilon_{max.}$	16,000, 16,000	1300, 700	
<i>m</i> -Me	$\lambda_{max.}$, A.	2510, 2550	2880, 2960	
	$\epsilon_{max.}$	17,500, 17,500	1300, 900	
<i>p</i> -Me	$\lambda_{max.}$, A.	2460, 2510, 2550	2890	
	$\epsilon_{max.}$	19,000, 22,000, 22,000	1600	
<i>p</i> -F	$\lambda_{max.}$, A.	2480, 2580	2800, 2950	
	$\epsilon_{max.}$	21,000, 15,000	1500, 800	
<i>p</i> -Cl	$\lambda_{max.}$, A.	2510, 2560, 2590	2900, 2990	
	$\epsilon_{max.}$	22,500, 23,000, 23,000	1700, 1150	
<i>p</i> -Br	$\lambda_{max.}$, A.	2580	2880, 2990	
	$\epsilon_{max.}$	26,000	2300, 1150	
<i>p</i> -MeO	$\lambda_{max.}$, A.	2610, 2690	2920	
	$\epsilon_{max.}$	25,000, 19,800	3400	

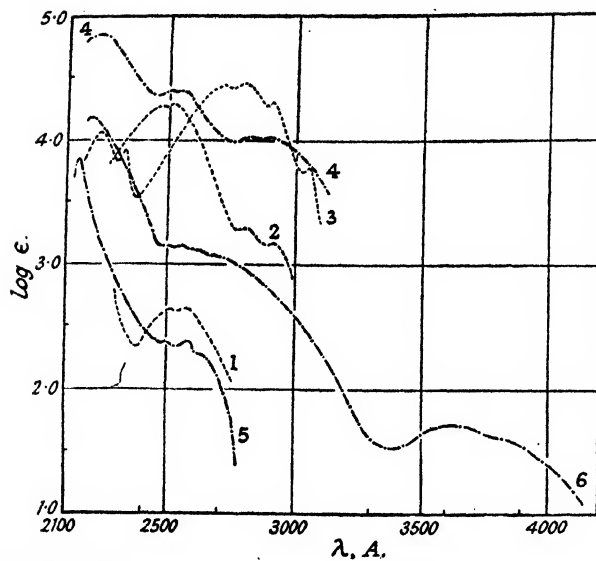
TABLE III.
Ultra-violet light absorption of $C_{10}H_7 \cdot NH \cdot CO_2 \cdot CHMe \cdot CH \cdot CH \cdot C_6H_4R$ in ethanol.

R.				
H	$\lambda_{max.}$, A.	2220	2510, 2560	2810, 2900
	$\epsilon_{max.}$	72,000	25,000, 25,000	10,000, 10,000
<i>o</i> -Me	$\lambda_{max.}$, A.	2210	2510	2810, 2910
	$\epsilon_{max.}$	76,000	20,000	9000, 9000
<i>m</i> -Me	$\lambda_{max.}$, A.	2200	2550	2810, 2910
	$\epsilon_{max.}$	75,000	20,000	8600, 8000
<i>p</i> -Me	$\lambda_{max.}$, A.	2210	2550	2800, 2900, 2960
	$\epsilon_{max.}$	69,000	20,000	11,000, 9600, 930
<i>p</i> -F	$\lambda_{max.}$, A.	2220	2500	2820, 2910
	$\epsilon_{max.}$	71,000	22,000	7500, 7500
<i>p</i> -Cl	$\lambda_{max.}$, A.	2220	2580	2910
	$\epsilon_{max.}$	68,000	30,000	10,500
<i>p</i> -Br	$\lambda_{max.}$, A.	2220	2580	2900
	$\epsilon_{max.}$	71,000	29,000	10,500
<i>p</i> -MeO	$\lambda_{max.}$, A.	2220	2650	2920
	$\epsilon_{max.}$	71,000	35,000	13,000

Ultra-violet light absorption of $C_{10}H_7 \cdot NH \cdot CO_2Me$ in ethanol for comparison.

$\lambda_{max.}$, A.	2230	—	2810, 2910
$\epsilon_{max.}$	68,000	—	6800, 6800

FIG. 1.



1. $\text{Ph}\cdot\text{CH}(\text{OH})\cdot\text{CH}\cdot\text{CHMe}$.
2. $\text{Ph}\cdot\text{CH}\cdot\text{CH}\cdot\text{CH}(\text{OH})\cdot\text{Me}$.
3. $\text{Ph}\cdot\text{CH}\cdot\text{CH}\cdot\text{CH}\cdot\text{CH}_3$.
4. $\text{Ph}\cdot\text{CH}\cdot\text{CHMe}\cdot\text{O}\cdot\text{CO}\cdot\text{NH}\cdot\text{Naphthyl}$.

(In ethanol.)

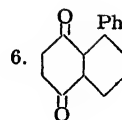
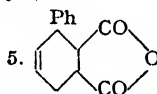
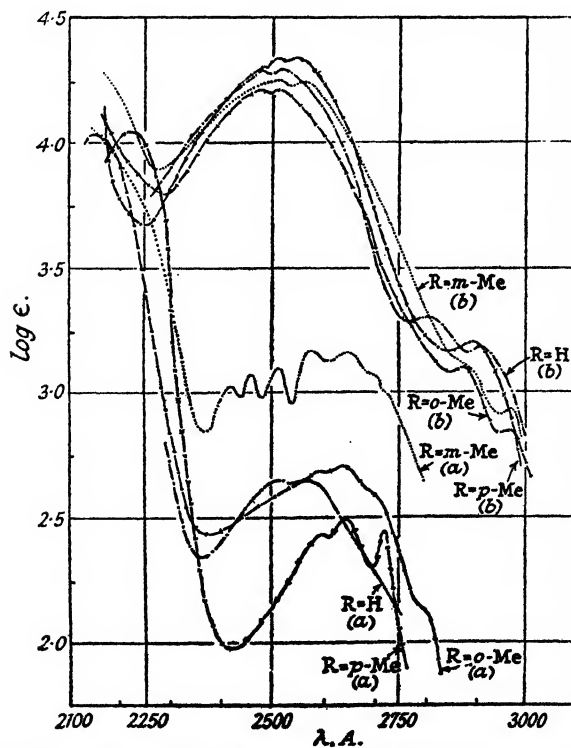


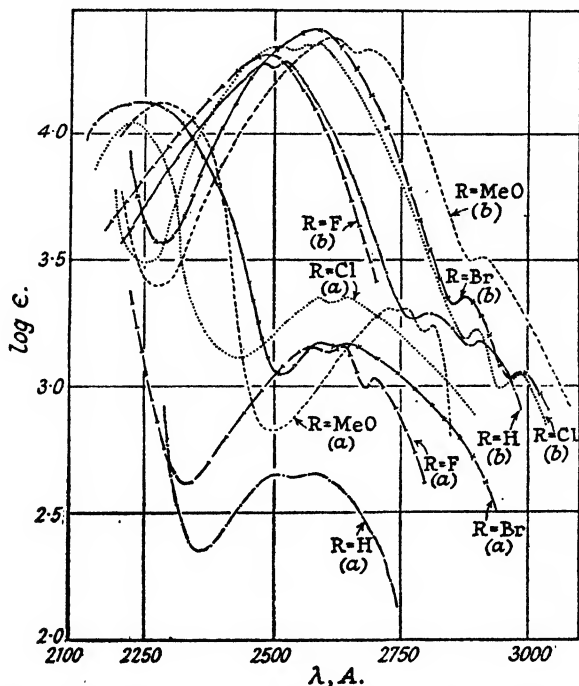
FIG. 2.



- (a) $\text{R}\cdot\text{C}_6\text{H}_4\cdot\text{CH}(\text{OH})\cdot\text{CH}\cdot\text{CHMe}$ and (b) $\text{R}\cdot\text{C}_6\text{H}_4\cdot\text{CH}\cdot\text{CH}\cdot\text{CH}(\text{OH})\text{Me}$.
(In ethanol.)

The phenylbutadienes (Table IV, Figs. 4 and 5) give rise to resolved absorption bands around 2200, 2800, and 3100 Å. The last two may be ascribed respectively to the phenylbutadiene and to the partial phenyl chromophore, while the first probably represents a summation of the low wave-length phenyl bands and absorption due to the partial butadiene chromophore. The effects of methyl, chloro-, and bromo-substituents on the 2800 Å. bands is smaller even than in the styryl system, while the fluoro-group again has a hypsochromic effect of 30 Å., and the methoxy-group a bathochromic effect of 110 Å. In the maleic anhydride

FIG. 3.



(a) $p\text{-R}\cdot\text{C}_6\text{H}_4\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{CHMe}$ and (b) $p\text{-R}\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}\cdot\text{CH}(\text{OH})\text{Me}$.
(In ethanol.)

adducts (Table V), the phenylchromophore is again isolated from the other unsaturated groups in the molecule and the absorption is very similar to that of the phenylpropenylcarbinols. The absorption curves of the benzoquinone adducts (Table VI) are a summation of those due

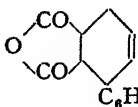
TABLE IV.

Ultra-violet light absorption of $\text{C}_6\text{H}_4\text{R}\cdot\text{CH}:\text{CH}\cdot\text{CH}:\text{CH}_2$ in ethanol.

R.				
H	$\lambda_{\text{max.}}$, Å.	2230, 2330	2710, 2800, 2900	3050
	$\epsilon_{\text{max.}}$	12,000, 8500	28,000, 28,300, 27,000	6000
<i>o</i> -Me	$\lambda_{\text{max.}}$, Å.	2230	2810	*
	$\epsilon_{\text{max.}}$	12,500	25,000	
<i>m</i> -Me	$\lambda_{\text{max.}}$, Å.	2170, 2285, 2350	2790	3110
	$\epsilon_{\text{max.}}$	16,600, 14,400, 10,000	29,000	7200
<i>p</i> -Me	$\lambda_{\text{max.}}$, Å.	2270, 2340	2730, 2810, 2880	3090
	$\epsilon_{\text{max.}}$	11,300, 9250	28,900, 30,000, 28,000	8000
<i>p</i> -F	$\lambda_{\text{max.}}$, Å.	2180	2730, 2770	*
	$\epsilon_{\text{max.}}$	12,800	30,000, 30,000	
<i>p</i> -Cl	$\lambda_{\text{max.}}$, Å.	2270, 2340	2810, 2860	3120
	$\epsilon_{\text{max.}}$	12,200, 7500	32,000, 31,000	5700
<i>p</i> -Br	$\lambda_{\text{max.}}$, Å.	2200, 2270	2810, 2860	*
	$\epsilon_{\text{max.}}$	13,600, 12,000	31,000, 30,000	
<i>p</i> -MeO	$\lambda_{\text{max.}}$, Å.	2220	2840, 2910	*
	$\epsilon_{\text{max.}}$	16,000	35,000, 35,000	

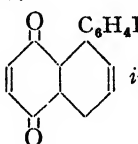
* Absorption beyond 3100 Å. not determined.

TABLE V.

Ultra-violet light absorption of  in ethanol.

R.				R.			
H	$\lambda_{\max.}$, A.	2,150	2480, 2580, 2650	<i>p</i> -Cl	$\lambda_{\max.}$, A.	2,230	2470, 2600, 2670,
	$\epsilon_{\max.}$	7,800	260, 270, 190				2770
<i>o</i> -Me	$\lambda_{\max.}$, A.	2,130	2630, 2710		$\epsilon_{\max.}$	12,500	280, 320, 350, 250
	$\epsilon_{\max.}$	11,500	250, 160	<i>p</i> -Br	$\lambda_{\max.}$, A.	2,230	2600, 2660, 2770
<i>m</i> -Me	$\lambda_{\max.}$, A.	2,145	2650, 2730		$\epsilon_{\max.}$	14,000	350, 350, 200
	$\epsilon_{\max.}$	11,000	330, 260	<i>p</i> -MeO	$\lambda_{\max.}$, A.	2,280	2650, 2700, 2720,
<i>p</i> -Me	$\lambda_{\max.}$, A.	2,180	2600, 2640, 2730				2760, 2820
	$\epsilon_{\max.}$	10,000	320, 350, 320		$\epsilon_{\max.}$	11,500	200, 270, 270, 270,
<i>p</i> -F	$\lambda_{\max.}$, A.	—	2600, 2650, 2710				230
	$\epsilon_{\max.}$	—	120, 155, 135				

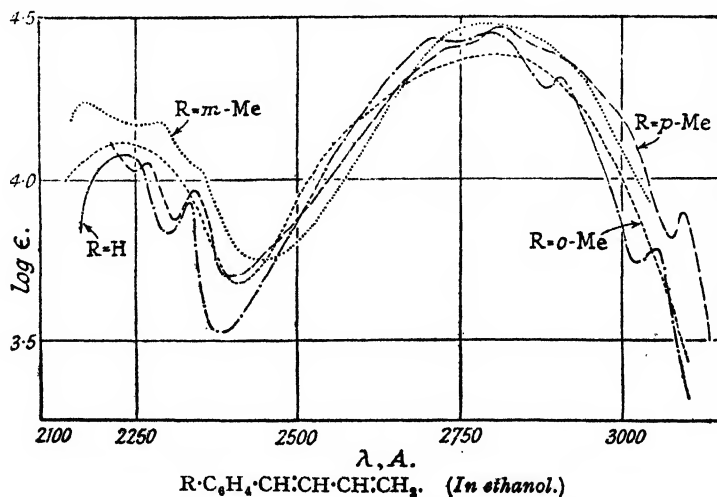
TABLE VI.

Ultra-violet light absorption of  in *n*-hexane.

R.					
H	$\lambda_{\max.}$, A.	2,200.	2500, 2560, 2610, 2690	3640, 3780	
	$\epsilon_{\max.}$	15,500	1450, 1400, 1300, 1100	53, 43	
<i>o</i> -Me	$\lambda_{\max.}$, A.	2,200	2600, 2810, 2910	3650	
	$\epsilon_{\max.}$	16,500	1400, 1100, 1100	60	
<i>p</i> -Me	$\lambda_{\max.}$, A.	2,220	2580, 2820	3640, 3760	
	$\epsilon_{\max.}$	19,000	1650, 850	55, 50	
<i>p</i> -F	$\lambda_{\max.}$, A.	2,180	2550, 2600, 2900	3650	
	$\epsilon_{\max.}$	23,000	2600, 1800, 850	80	
<i>p</i> -Cl	$\lambda_{\max.}$, A.	2,250	2550, 2820, 2920	3650	
	$\epsilon_{\max.}$	24,000	1500, 900, 900	55	
<i>p</i> -Br	$\lambda_{\max.}$, A.	2,230, 2,270	2490, 2560	3650	
	$\epsilon_{\max.}$	27,500, 27,000	2400, 2000	55	

to their separate phenyl and dihydro-quinone systems, the latter giving rise to bands near 2500 and 3600 A., *i.e.*, displaced by *ca.* 200 A. with respect to those shown by the open-chain diacetyl-ethylene system (Braude, *J.*, 1945, 490) (Fig. 1).

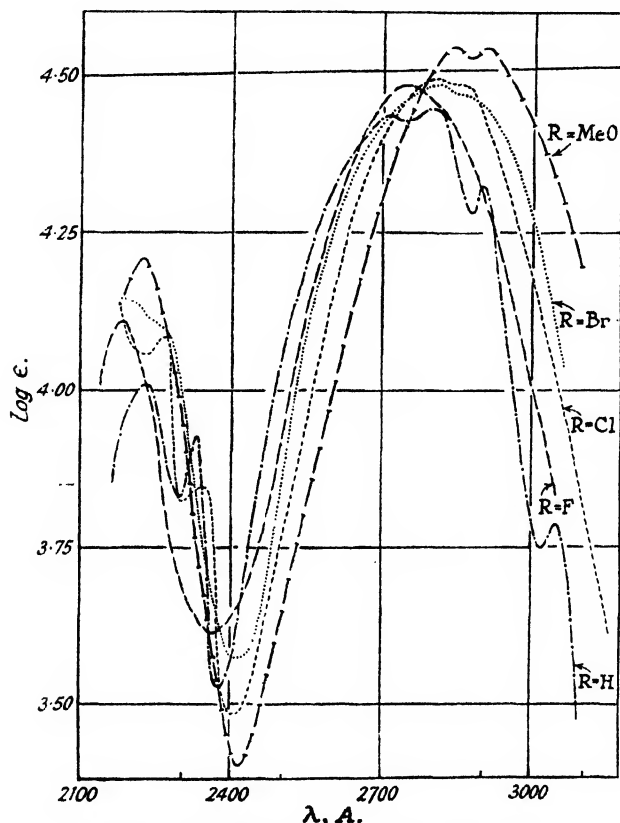
FIG. 4.



The variochromic effects of the nuclear substituents on the principal bands in the phenyl-propenylcarbinols, styrylmethylcarbinols, and phenylbutadienes are summarised in Table VII.

(The exact values of $\Delta\lambda$ are somewhat arbitrary owing to the vibrational structure. The highest peaks have been taken as characteristic of a group, and where two peaks of equal intensity are shown, the one at higher wave-length has been used for computing $\Delta\lambda$.) These effects are generally smallest (10–50 Å.) for a methyl substituent, a little larger (10–90 Å.) for the halogen groups, and largest (70–180 Å.) for the methoxyl group. A number of other regularities appear, but their generality is too limited to warrant separate discussion. The fact, however, that the variochromic effects of nuclear substituents in the styryl and phenylbutadiene systems are no greater than in the phenyl one and smaller than in corresponding

FIG. 5.



$p\text{-R-C}_6\text{H}_4\text{-CH:CH-CH:CH}_2$. (In ethanol.)

TABLE VII.

The variochromic effects of nuclear substituents.

R.	"Phenyl" band.	$\text{C}_6\text{H}_4\text{R-CH(OH)-CH:CHMe} : \text{C}_6\text{H}_4\text{R-CH:CH-CH(OH)Me} : \text{C}_6\text{H}_4\text{R-CH:CH-CH:CH}_2 :$			
		"Styrene" band.	"Phenyl" band.	"Phenylbutadiene" band.	"Phenyl" band.
H	2580	$\lambda_{\text{max.}}$ A. 2510	2810	2800	3050
		$\Delta\lambda_{\text{max.}}$ A.			
<i>o</i> -Me	+ 60	+ 40	+ 70	+ 10	—
<i>m</i> -Me	+ 50	+ 40	+ 70	— 10	+ 60
<i>p</i> -Me	+ 65	+ 40	+ 80	+ 10	+ 40
<i>p</i> -F	+ 60	— 30	— 10	— 30	—
<i>p</i> -Cl	+ 60	+ 80	+ 90	+ 10	+ 70
<i>p</i> -Br	+ 70	+ 70	+ 70	+ 10	—
<i>p</i> -MeO	+ 180	+ 100	+ 110	+ 110	—

systems where the substituents are directly attached to acyclic ethylenic double bonds (cf. Bowden, Braude, and Jones, *J.*, 1946, 948) is of interest. Since the conjugating and transmitting capacity of a group is related to its polarisability (cf. Braude, *loc. cit.*), it provides spectral evidence for the lower polarisability of the phenyl nucleus as compared with an aliphatic ethylenic group.

EXPERIMENTAL.

(Light-absorption data are only given when not included in Tables I—VI.)

o-Tolylpropenylcarbinol (I; R = *o*-Me).—Freshly distilled crotonaldehyde (20 g.) in ether (40 c.c.) was added to *o*-tolylmagnesium bromide (from Mg, 6.5 g.) in ether (250 c.c.) during one hour at 0°; the solution was then stirred for 3 hours and treated with excess of ammonium chloride solution. Isolation of the product with ether, drying over anhydrous potassium carbonate, and distillation from a trace of potassium carbonate yielded *o*-tolylpropenylcarbinol (30.5 g.), b. p. 61°/0.001 mm., n_D^{20} 1.5392 (Found: C, 81.2; H, 8.7. $C_{11}H_{14}O$ requires C, 81.45; H, 8.7%).

o-Methylstyrylmethylcarbinol (II; R = *o*-Me).—Treatment of the above carbinol (1.5 g.) with 0.01M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 12 hours at 30° yielded *o*-methylstyrylmethylcarbinol (1.35 g.), b. p. 66°/0.005 mm., n_D^{20} 1.5590 (Found: C, 81.75; H, 8.55. $C_{11}H_{14}O$ requires C, 81.45; H, 8.7%). The *α*-naphthylurethane (0.6 g.), obtained by treating the carbinol (0.33 g.) with *α*-naphthyl isocyanate (0.35 g.), crystallised from petrol (b. p. 80–100°) in needles, m. p. 104° (Found: C, 79.9; H, 6.5; N, 4.2. $C_{22}H_{21}O_2N$ requires C, 79.75; H, 6.4; N, 4.2%).

1-(*o*-Tolyl)buta-1 : 3-diene.—*o*-Tolylpropenylcarbinol (4 g.) was distilled from potassium hydrogen sulphate (0.8 g.) at 10⁻² mm. The diene after fractionation had b. p. 37°/0.01 mm., n_D^{20} 1.6008 (Found: C, 91.0; H, 8.5. $C_{11}H_{12}$ requires C, 91.6; H, 8.4%). The maleic anhydride adduct (0.65 g.) was obtained by refluxing the diene (0.5 g.) with maleic anhydride (0.25 g.) in benzene (3 c.c.) for 5 minutes. It crystallised from petrol (b. p. 80–100°) in fine needles, m. p. 92° (Found: C, 73.9; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.3%).

p-Benzoquinone adduct. A solution of the diene (5.0 g.) and *p*-benzoquinone (3.5 g.) in benzene (15 c.c.) was boiled for a few minutes. On cooling, and evaporation of the solvent under reduced pressure, crystals separated which were washed with a little methanol to remove a small amount of quinhydrone. Recrystallisation from petrol (b. p. 80–100°) afforded pale yellow plates of 1-(*o*-tolyl)-1 : 4 : 9 : 10-tetrahydronaphthaquinone (3.7 g.), m. p. 93.5° (Found: C, 80.9; H, 6.25. $C_{17}H_{16}O_2$ requires C, 80.95; H, 6.4%). On allowing the quinone (1 g.) to stand overnight with acetic anhydride (25 g.) and zinc chloride (0.5 g.) and dilution with water, 1-(*o*-tolyl)-1 : 4-dihydronaphthaquinol diacetate (1 g.) was obtained; it crystallised from petrol (b. p. 80–100°) or alcohol, and had m. p. 141° (Found: C, 74.9; H, 6.1. $C_{22}H_{20}O_4$ requires C, 74.9; H, 6.0%). Light absorption in alcohol: Maxima at 2180, 2650, and 2720 Å., ϵ = 25,000, 800, and 720, respectively.

m-Tolylpropenylcarbinol (I; R = *m*-Me).—Freshly distilled crotonaldehyde (9.5 g.) in ether (50 c.c.) was added to *m*-tolylmagnesium bromide (from Mg, 3.2 g.) during one hour at 0°, and the solution stirred for 3 hours. Working up in the usual manner and distillation from a trace of potassium carbonate yielded *m*-tolylpropenylcarbinol (17 g.), b. p. 76°/0.01 mm., n_D^{20} 1.5384 (Found: C, 81.8; H, 8.7. $C_{11}H_{14}O$ requires: C, 81.45; H, 8.7%).

m-Methylstyrylmethylcarbinol (II; R = *m*-Me).—Treatment of the above carbinol (1.5 g.) with 0.01M-hydrochloric acid in 60% dioxan (50 c.c.) for 24 hours at 30° yielded *m*-methylstyrylmethylcarbinol (1.30 g.), b. p. 69°/0.005 mm., n_D^{20} 1.5608 (Found: C, 81.7; H, 8.65. $C_{11}H_{14}O$ requires C, 81.45; H, 8.7%). The *α*-naphthylurethane crystallised from petrol (b. p. 80–100°); m. p. 96° (Found: C, 79.8; H, 6.6; N, 4.2. $C_{22}H_{21}O_2N$ requires C, 79.75; H, 6.4; N, 4.25%).

1-(*m*-Tolyl)buta-1 : 3-diene.—*m*-Tolylpropenylcarbinol (2.5 g.) was distilled from potassium hydrogen sulphate (0.25 g.) at 10⁻² mm. Fractionation of the product from potassium hydrogen sulphate (0.1 g.) yielded the diene (1.8 g.), b. p. 80°/0.005 mm., n_D^{20} 1.5980 (Found: C, 89.5; H, 8.5. $C_{11}H_{12}$ requires C, 91.6; H, 8.4%). The maleic anhydride adduct was obtained by treating the diene (0.5 g.) with maleic anhydride (0.3 g.) in benzene (3 c.c.). Crystallisation from light petroleum (b. p. 60–80°) yielded the adduct (0.7 g.) in long needles, m. p. 78° (Found: C, 74.35; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%).

p-Tolylpropenylcarbinol (I; R = *p*-Me).—Freshly distilled crotonaldehyde (35 g.) in ether (70 c.c.) was added to *p*-tolylmagnesium bromide (from Mg, 12 g.) in ether (300 c.c.) during one hour at 0°, and the solution stirred for 3 hours. Isolation of the product in the usual manner afforded *p*-tolylpropenylcarbinol (65 g.), which crystallised from light petroleum (b. p. 40–60°) in needles, m. p. 55° (Found: C, 81.55; H, 8.65. $C_{11}H_{14}O$ requires C, 81.45; H, 8.7%).

p-Methylstyrylmethylcarbinol (II; R = *p*-Me).—Treatment of the above carbinol (1 g.) with 0.001M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 15 hours at 30° yielded *p*-methylstyrylmethylcarbinol (0.86 g.), which crystallised from light petroleum (b. p. 40–60°) in needles, m. p. 43° (Found: C, 81.3; H, 8.55. $C_{11}H_{14}O$ requires C, 81.45; H, 8.7%). The *α*-naphthylurethane crystallised from petrol (b. p. 80–100°) in needles, m. p. 135°, or from methanol, m. p. 127° (Found: C, 79.45; H, 6.4; N, 4.05. $C_{22}H_{21}O_2N$ requires C, 79.75; H, 6.4; N, 4.25%).

1-(*p*-Tolyl)buta-1 : 3-diene.—*p*-Tolylpropenylcarbinol (2 g.) was distilled from potassium hydrogen sulphate (0.2 g.) at 10⁻² mm. The diene, b. p. 78°/0.005 mm., solidified at room temperature and after crystallisation from aqueous methanol had m. p. 26° (Found: C, 90.6; H, 8.55. $C_{11}H_{12}$ requires C, 91.6; H, 8.4%). The maleic anhydride adduct was obtained by treating the diene (1.5 g.) with maleic anhydride (1 g.) in benzene (10 c.c.). Crystallisation from petrol (b. p. 80–100°) yielded the adduct (2.3 g.) in long needles, m. p. 117° (Found: C, 74.6; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%).

p-Benzoquinone adduct. Treatment of the diene (2.2 g.) with *p*-benzoquinone (1.8 g.) in benzene (10 c.c.) afforded *p*-tolyl-1 : 4 : 9 : 10-tetrahydronaphtha-5 : 8-quinone (2.8 g.), which crystallised from

petrol (b. p. 80–100°) in pale yellow plates, m. p. 114° (Found: C, 81.4; H, 6.3. $C_{17}H_{14}O_2$ requires C, 81.0; H, 6.4%).

p-Fluorophenylpropenylcarbinol (I, R = *p*-F).—*p*-Bromofluorobenzene (58 g.) (Schieman and Pilarsky, *Ber.*, 1931, 64, 1343) in ether (250 c.c.) was added slowly to a suspension of magnesium (8.0 g.) in ether (150 c.c.) containing ethyl bromide (0.5 g.) and stirred for 4 hours in an atmosphere of nitrogen. Freshly distilled crotonaldehyde (23 g.) in ether (50 c.c.) was added to the ice-cold suspension during 2 hours, and stirring continued overnight. On working up in the usual manner, *p*-fluorophenylpropenylcarbinol (37 g.) was obtained, b. p. 59°/0.001 mm., n_D^{20} 1.5175 (Found: C, 72.2; H, 7.0. $C_{18}H_{11}OF$ requires C, 72.25; H, 6.7%). Active hydrogen (Zerewitinoff): 1.02.

p-Fluorostyrylmethylcarbinol (II; R = *p*-F).—Treatment of the above carbinol (1.5 g.) with 0.01M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 36 hours at 30° yielded *p*-fluorostyrylmethylcarbinol (1.4 g.), b. p. 78°/0.01 mm., n_D^{20} 1.5411, which solidified on standing at room temperature and after crystallisation from light petroleum (b. p. 40–60°) had m. p. 42° (Found: C, 72.3; H, 6.95. $C_{10}H_{11}OF$ requires C, 72.25; H, 6.7%). The α -naphthylurethane crystallised from petrol (b. p. 80–100°) in needles, m. p. 116° (Found: C, 75.5; H, 5.7; N, 4.1. $C_{21}H_{18}O_2NF$ requires C, 75.2; H, 5.4; N, 4.2%).

1-(*p*-Fluorophenyl)buta-1:3-diene.—*p*-Fluorophenylpropenylcarbinol (2.5 g.) was distilled from potassium hydrogen sulphate (0.25 g.) at 10⁻² mm. The product was fractionated from potassium hydrogen sulphate (0.1 g.) and *p*-fluorophenylbutadiene (1.7 g.) was obtained, b. p. 37°/0.001 mm., n_D^{22} 1.5788, which solidified on cooling and had m. p. 16–16.5° (Found: C, 80.4; H, 6.6. $C_{10}H_9F$ requires C, 80.65; H, 6.5%). The maleic anhydride adduct (0.25 g.) was obtained by treating the diene (0.18 g.) with maleic anhydride (0.12 g.) in benzene (5 c.c.). Crystallisation from petrol (b. p. 80–100°) yielded the adduct in needles, m. p. 113° (Found: C, 68.5; H, 4.7. $C_{14}H_{11}O_3F$ requires C, 68.3; H, 4.5%).

p-Benzoquinone adduct. The diene (1.2 g.) was treated with *p*-benzoquinone (0.67 g.) in benzene (5 c.c.). Crystallisation from petrol (b. p. 80–100°) afforded 1-*p*-fluorophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone (0.93 g.) as very pale yellow needles, m. p. 90° (Found: C, 74.8; H, 5.3. $C_{18}H_{13}O_2F$ requires C, 75.0; H, 5.1%).

p-Chlorophenylpropenylcarbinol (I; R = *p*-Cl).—*p*-Dichlorobenzene (74 g.) in ether (400 c.c.) was slowly added to a suspension of magnesium (12 g.) in ether (100 c.c.) containing ethyl bromide (0.5 g.) and refluxed for 96 hours. Freshly distilled crotonaldehyde (35 g.) in ether (70 c.c.) was added during one hour at 0°, and the solution was stirred for 3 hours. Working up in the usual manner yielded unchanged *p*-dichlorobenzene (23 g.) and *p*-chlorophenylpropenylcarbinol (28 g.), b. p. 89°/0.005 mm., n_D^{21} 1.5471 (Found: C, 65.9; H, 6.2; Cl, 19.3. $C_{10}H_{11}OCl$ requires C, 65.7; H, 6.05; Cl, 19.4%). Active hydrogen (Zerewitinoff): 1.02.

p-Chlorostyrylmethylcarbinol (II; R = *p*-Cl).—Treatment of the above carbinol (1 g.) with 0.01M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 40 hours at 30° yielded *p*-chlorostyrylmethylcarbinol (0.87 g.), which separated from light petroleum (b. p. 40–60°) in needles, m. p. 63° (Found: C, 65.95; H, 6.0. $C_{10}H_{11}OCl$ requires C, 65.75; H, 6.1%). α -Naphthylurethane. (i) A mixture of *p*-chlorostyrylmethylcarbinol (0.5 g.) and α -naphthyl isocyanate (0.5 g.) was kept in a sealed tube for 5 days. The urethane crystallised from petrol (b. p. 80–100°) in needles, m. p. 128° (Found: C, 71.5; H, 5.35. $C_{21}H_{18}O_2NCl$ requires C, 71.6; H, 5.6%). (ii) *p*-Chlorophenylpropenylcarbinol (0.5 g.) was treated with α -naphthyl isocyanate (0.5 g.). The oily product after one crystallisation from aqueous ethanol had m. p. 69°. On successive crystallisations from ethanol and finally petrol, the m. p. rose to 128° [undepressed by the product obtained under (i)], and the light absorption maximum, not originally present, at 2580 Å., ϵ = 30,000 (see Table III), appeared.

1-(*p*-Chlorophenyl)buta-1:3-diene.—*p*-Chlorophenylpropenylcarbinol (2 g.) was distilled from potassium hydrogen sulphate (0.5 g.) at 10⁻² mm., and the product fractionated. The diene (1.55 g.), b. p. 49°/0.002 mm., n_D^{20} 1.6202, solidified on cooling and had m. p. 18.5° (Found: Cl, 21.75. $C_{10}H_9Cl$ requires Cl, 21.55%). The maleic anhydride adduct, obtained by the routine method and crystallised from petrol (b. p. 80–100°), had m. p. 108° (Found: Cl, 13.3. $C_{14}H_{11}O_3Cl$ requires Cl, 13.5%).

p-Benzoquinone adduct. Treatment of the diene (1.6 g.) with *p*-benzoquinone (1.2 g.) yielded the pale yellow adduct, 1-*p*-chlorophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone (1.8 g.); after being washed with methanol and crystallised from petrol (b. p. 80–100°) it had m. p. 110° (Found: C, 70.35; H, 4.8; Cl, 12.85. $C_{18}H_{13}O_2Cl$ requires C, 70.45; H, 4.8; Cl, 13.0%).

p-Bromophenylpropenylcarbinol (I; R = *p*-Br).—*p*-Dibromobenzene (60 g.) in ether (150 c.c.) was slowly added to a suspension of magnesium (6 g.) in ether (100 c.c.) containing ethyl bromide (0.5 g.) and refluxed for 24 hours. Freshly distilled crotonaldehyde (17 g.) in ether (50 c.c.) was added during one hour at 0° and the solution was stirred for 3 hours. Working up in the usual manner yielded unchanged *p*-dibromobenzene (5 g.) and *p*-bromophenylpropenylcarbinol (26 g.), b. p. 92°/0.002 mm., n_D^{21} 1.5739, which solidified on cooling and after crystallisation from light petroleum (b. p. 40–60°) had m. p. 27° (Found: C, 52.7; H, 5.15; Br, 36.0. $C_{10}H_{11}OBr$ requires C, 52.9; H, 4.9; Br, 35.2%).

p-Bromostyrylmethylcarbinol (II; R = *p*-Br).—Treatment of the above carbinol (1.5 g.) with 0.1M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 12 hours yielded *p*-bromostyrylmethylcarbinol (1.4 g.) as needles, from light petroleum (b. p. 40–60°), m. p. 66° (Found: C, 53.2; H, 5.0. $C_{10}H_{11}OBr$ requires C, 52.9; H, 4.9%). The α -naphthylurethane (0.55 g.) crystallised from petrol (b. p. 80–100°) in needles, m. p. 139° (Found: C, 64.0; H, 4.55; N, 3.85. $C_{21}H_{18}O_2NBr$ requires C, 63.65; H, 4.55; N, 3.55%).

1-(*p*-Bromophenyl)buta-1:3-diene.—*p*-Bromophenylpropenylcarbinol (2 g.) was distilled from potassium hydrogen sulphate (0.5 g.) at 10⁻² mm. The product was fractionated, giving the diene (1.5 g.), b. p. 88°/0.001 mm., which solidified at room temperature, and crystallised from aqueous methanol; m. p. 29° (Found: C, 57.05; H, 4.7. $C_{10}H_9Br$ requires C, 57.45; H, 4.35%). The maleic anhydride adduct, obtained as usual and crystallised from petrol (b. p. 80–100°), formed fine needles, m. p. 138.5° (Found: C, 55.0; H, 3.65. $C_{14}H_{11}O_3Br$ requires C, 54.75; H, 3.6%).

p-Benzoquinone adduct. Treatment of the diene (0.5 g.) with *p*-benzoquinone (0.25 g.) in benzene (5 c.c.) gave the adduct, 1-*p*-bromophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone (0.45 g.), which

crystallised from petrol (b. p. 80–100°) in pale yellow rectangular plates, m. p. 105° (Found : C, 60.4; H, 3.95. $C_{14}H_{14}O_2$ requires C, 60.6; H, 4.15%).

p-Anisylpropenylcarbinol (I; R = *p*-MeO).—*p*-Bromoanisole (35 g.) in ether (100 c.c.) was added slowly to a suspension of magnesium (4.45 g.) in ether (250 c.c.) containing ethyl bromide (0.5 g.) and stirred overnight in an atmosphere of nitrogen. Freshly distilled crotonaldehyde (12 g.) in ether (25 c.c.) was added during one hour at 0° and the solution was stirred for 3 hours. Working up in the usual manner and final distillation from a trace of potassium carbonate yielded *p*-anisylpropenylcarbinol (23.5 g.), b. p. 100°/0.005 mm., n_D^{20} 1.5454, which partly solidified on standing at 0°; m. p. 13–15° (Found : C, 74.45; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.9%). Active hydrogen (Zerewitinoff) : 1.01.

p-Methoxystyrylmethylcarbinol (II; R = *p*-MeO).—Treatment of the above carbinol (1 g.) with 0.001M-hydrochloric acid in 60% aqueous dioxan (50 c.c.) for 3 hours at 30° yielded *p*-methoxystyrylmethylcarbinol (0.95 g.), in needles from light petroleum (b. p. 40–60°); m. p. 79° (Found : C, 73.95; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.9%). Active hydrogen (Zerewitinoff) : 1.02. The *α*-naphthylurethane (0.4 g., 0.8 g. respectively) was obtained by warming (i) *p*-anisylpropenylcarbinol (0.5 g.) and (ii) *p*-methoxystyrylmethylcarbinol (0.5 g.) with *α*-naphthyl isocyanate (0.5 g.), and crystallised from petrol (b. p. 80–100°) in needles, m. p. 101° (Found : N, 4.1. $C_{22}H_{21}O_3N$ requires N, 4.05%).

1-(*p*-Anisyl)buta-1 : 3-diene.—*p*-Anisylpropenylcarbinol (1 g.) was warmed with potassium hydrogen sulphate at 10⁻² mm. for about 5 minutes, and then rapidly distilled. *p*-Anisylbutadiene (0.7 g.) solidified on standing and was crystallised from aqueous methanol, m. p. 46° (Found : C, 82.2; H, 7.45. $C_{11}H_{14}O$ requires C, 82.45; H, 7.55%). Knorr (D.R.-P. 544388; *Chem. Abs.*, 1932, 26, 2467) gives b. p. 124°/8 mm. for the diene obtained by dehydration of *p*-anisylallylcarbinol. The maleic anhydride adduct crystallised from petrol (b. p. 80–100°) in fine needles, m. p. 145° (Found : C, 70.0; H, 5.4. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%).

p-Benzoquinone adduct. Treatment of the diene (0.53 g.) with *p*-benzoquinone (0.33 g.) in benzene (5 c.c.) yielded 1-*p*-anisyl-1 : 4 : 9 : 10-tetrahydronaphthaquinone (0.38 g.), pale yellow plates from petrol (b. p. 80–100°); m. p. 103° (Found : C, 76.35; H, 6.0. $C_{17}H_{14}O_2$ requires C, 76.05; H, 6.0%). Light absorption in *n*-hexane : Maxima at 2280, 2680, and 3250 Å., ϵ = 23,300, 2500, and 230, respectively. The absorption may be ascribed to the isomer, 1-*p*-anisyl-1 : 4-dihydronaphtha-5 : 9-quinol (needles, m. p. 168°), which is produced on irradiation with ultra-violet light during the absorption measurements and separates from the solution on standing or evaporation.

1-Phenylbuta-1 : 3-diene.—Freshly distilled cinnamaldehyde (40 g.) in ether (120 c.c.) was added to methylmagnesium iodide (from Mg, 8 g.) in ether (200 c.c.). Decomposition of the complex with excess of ammonium chloride solution, isolation with ether, distillation from a trace of potassium hydrogen sulphate, and finally fractionation afforded pure phenylbutadiene, b. p. 45°/0.5 mm., n_D^{17} 1.6125, which solidified on cooling and had m. p. 4° (Klages, *Ber.*, 1904, 37, 2309, gives b. p. 86°/11 mm.; Muskat and Herrman, *J. Amer. Chem. Soc.*, 1931, 53, 252, give b. p. 86°/11 mm., n_D^{28} 1.5950; Emerson, *J. Org. Chem.*, 1945, 10, 464, gives b. p. 89–94°/14 mm., n_D^{25} 1.6010). The low refractive indices recorded by these authors are probably due to the presence of considerable proportions of undehydrated styrylmethylcarbinol or of polymers of the diene (cf. Stobbe and Reiss, *Ber.*, 1912, 45, 3496; Wright, *J. Org. Chem.*, 1936, 1, 457). Light absorption : see Table IV (Stobbe and Reiss, *loc. cit.*, and Smakula, *Angew. Chem.*, 1934, 47, 657, give maximum at 2800 Å., ϵ = 24,000). The maleic anhydride adduct, crystallised from petrol (b. p. 80–100°), had m. p. 120° (Diels and Alder, *Ber.*, 1929, 62, 2081, give m. p. 120°).

p-Benzoquinone adduct. Phenylbutadiene (2 g.) was treated with *p*-benzoquinone (2 g.) in benzene (20 c.c.), and the solution boiled for some minutes. On cooling and evaporation of the solvent under reduced pressure, crystals separated, which were washed with methanol to remove a small amount of quinhydrone. Phenyl-1 : 4 : 9 : 10-tetrahydronaphtha-5 : 8-quinone (2.25 g.) crystallised from petrol (b. p. 80–100°) in pale yellow rectangular plates, m. p. 101° (Found : C, 80.7; H, 5.9. $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.9%).

Styrylmethylcarbinol *α*-naphthylurethane. Prepared from styrylmethylcarbinol (Braude, Jones, and Stern, *J.*, 1946, 396) (0.5 g.) and *α*-naphthyl isocyanate (0.5 g.), the urethane crystallised from petrol (b. p. 80–100°) in needles, m. p. 89.5° (Found : C, 79.25; H, 6.1; N, 4.2. $C_{21}H_{19}O_3N$ requires C, 79.45; H, 6.05; N, 4.4%).

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[Received, November 26th, 1946].

206. The Kinetics of Anionotropic Rearrangement. Part VI. The Effects of Methyl, Methoxy-, and Halogen Substituents attached to a Phenyl Group.

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The kinetics of the acid-catalysed oxotropy of substituted phenylpropenylcarbinols to the corresponding styrylmethylcarbinols (p. 1097, I \rightarrow II) have been studied. The effects of nuclear substituents in this molecular rearrangement are in accord with those observed in substitution reactions and in the dissociation constants of substituted benzoic acids. The reaction is facilitated by methyl and methoxyl substituents, and retarded by halogen substituents, first-order rate constants at one temperature varying in the order *p*-Br < *p*-Cl < *p*-F < H < *m*-Me < *o*-Me < *p*-Me < *p*-MeO. The differences in the rate constants are due to small

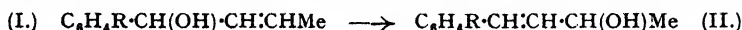
changes both in the isodielectric energy of activation and in the non-exponential factor of the Arrhenius equation. The results are discussed in terms of the electronic effects of the substituent groups and the unexpected sequence previously noted by other authors of tautomeric effects decreasing in the order $F > Cl > Br$, is confirmed.

IN previous papers in this series, detailed investigations have been described of rearrangements of the type where X is an acetylenic, ethylenic, or phenyl group. A reaction mechanism has



been outlined which accounts for the kinetic features of the reaction and their dependence on medium composition. The effects of many aliphatic substituents have been examined and found to be those expected for a reaction requiring electron accession at the point of reaction. It appeared worth while to extend this work to a study of the effects of aromatic substituents, data for which have hitherto been largely derived from substitution reactions and dissociation constants.

It was shown in Part V (*J.*, 1946, 396) that the rearrangement of phenylpropenylcarbinol (I, $R = H$) to styrylmethylcarbinol (II, $R = H$) proceeds smoothly in aqueous dioxan in the presence of hydrochloric acid, that the reaction follows the first-order law, and that the rate constants are practically independent of the carbinol concentration, roughly proportional to the acid concentration (c_A) when $c_A \ll 0.1M$, and decreased by increasing dioxan concentration (c_s) when $c_s \ll 80\%$ v/v. The same characteristics apply to the rearrangements of substituted



phenylpropenylcarbinols (I) where $R = o\text{-Me}$, $m\text{-Me}$, $p\text{-Me}$, $p\text{-F}$, $p\text{-Cl}$, $p\text{-Br}$, and $p\text{-MeO}$ (Tables I, II, and III). The rate constants determined at 10° intervals between 30° and 60° accurately obey the Arrhenius equation.

It was previously observed (Part V, *loc. cit.*) that in the rearrangements of phenylvinyl- and phenylpropenyl-carbinols, the highest extinction coefficients reached in kinetic runs were lower by some 3–8% than those of the pure styryl isomers isolated from the reaction mixture, and it was suggested that the formation of stereoisomers or the establishment of equilibria at 92–97% rearrangement was among the more likely explanations of the discrepancies. With

TABLE I.

The effect of carbinol concentration.

First-order rate constants (10^4k , min.^{-1}) for the rearrangement of $C_6H_4R \cdot CH(OH) \cdot CH:CHMe$ in 60% (by vol.) aqueous dioxan at 30.0° . c_{ROH} = carbinol concentration (% w/v); c_A = hydrochloric acid concentration (mols./l.).

R =	H.	<i>p</i> -Me.	<i>p</i> -Cl.	<i>p</i> -MeO.
c_{ROH} .	$c_A = 0.01M$.	$c_A = 0.001M$.	$c_A = 0.01M$.	$c_A = 0.0001M$.
0.020	185	154	40.0	179
0.10	184	161	40.8	185
0.500	180	157	36.2	177

TABLE II.

The effect of acid concentration.

First-order rate constants for the rearrangement of $C_6H_4R \cdot CH(OH) \cdot CH:CHMe$ in 60% (by vol.) aqueous dioxan at 30.0° . c_A = hydrochloric acid concentration (mols./l.).

c_A .	10^4k (min.^{-1}).	k/c_A .	c_A .	10^4k (min.^{-1}).	k/c_A .
R = H.			R = <i>p</i> -F.		
0.002	34.7	1.74	0.002	29.9	1.50
0.01	184	1.84	0.01	146	1.46
0.1	1760	1.76	0.1	1520	1.52
R = <i>p</i> -Me.			R = <i>p</i> -Cl.		
0.0001	15.0	15.0	0.001	4.34	0.434
0.001	161	16.1	0.01	40.8	0.410
0.01	1540	15.4	0.1	432	0.432
R = <i>p</i> -MeO.			R = <i>p</i> -Br.		
0.0001	185	185	0.001	3.40	0.340
0.001	1890	189	0.01	35.2	0.352
0.002	3660	183	0.1	365	0.365

TABLE III.

Temperature and solvent effects.

First-order rate constants ($10^4 k$, min.⁻¹) for the rearrangement of $C_6H_5R \cdot CH(OH) \cdot CH:CH \cdot CH_3$. Carbinol concentration 0.1% (w/v) throughout. c_A = Hydrochloric acid concentration (mols./l.). c_s = Dioxan concentration (% v/v).

<i>t</i> .	<i>c_s</i>	R = H. <i>c_A</i> = 0.01	<i>o</i> -Me. 0.001	<i>m</i> -Me. 0.001	<i>p</i> -Me. 0.001	<i>p</i> -F. 0.01	<i>p</i> -Cl. 0.01	<i>p</i> -Br. 0.01	<i>p</i> -MeO. 0.0001
0.0°	40	25.5	5.17	2.96	22.9	19.2	4.60	3.59	177
	60	5.40	1.18	0.56	3.98	3.62	0.83	0.75	31.5
30.0	40	716	139	80.9	406	580	135	127	647
	60	184	35.9	21.7	161	146	40.8	35.2	185
40.0	40	1,890	382	163	1,300	1550	436	364	1340
	60	545	127	62.7	414	401	99.8	94.5	521
50.0	40	4,500	840	408	3,060	3900	1070	865	2960
	60	1,510	281	195	1,080	1200	302	272	1290
60.0	40	11,700	2350	1380	10,200	9390	2770	2350	5930
	60	3,650	910	571	2,900	2902	908	778	2780

the substituted phenylpropenylcarbinols, the ratios of "kinetic" to "preparative" end-values vary from 0.87 to 0.97, and are again temperature-independent within the experimental error ($\pm 2\%$) (see Experimental). Now, since the type and number of bonds broken and formed in the reaction is otherwise equal and opposite, the heat of reaction should be of the same order as the additional resonance energy of the conjugated (styryl) system, *i.e.* ca. 5 kg.-cals./mol. (Pauling and Sherman, *J. Chem. Physics*, 1933, 1, 606; Kistiakowsky, Ruhoff, Smith, and Vaughan, *J. Amer. Chem. Soc.*, 1936, 58, 146). This corresponds to an approximately two-fold change in the equilibrium constant for a temperature change from 30° to 60°, and to a change in conversion from 95 to 90%, *i.e.*, only just more than the limit of experimental error. The present data are thus indecisive. If equilibrium formation does take place, the over-all rate constants k actually represent the sum ($k_1 + k_{-1}$) of the rate constants of the forward and backward reactions $ROH \xrightleftharpoons[k_{-1}]{k_1} R'OH$, but the values of k_1 will only be 3–13% lower than those of k , and the values of the Arrhenius parameters will hardly be affected.

It was pointed out in Part II (*J.*, 1944, 443) that two types of solvent effect may be distinguished in considering the dependence of the rate constants, energies of activation, etc., of a catalysed reaction on the reaction medium. Those directly affecting the reactants were termed primary solvent effects, while those resulting in the first place in a change in the catalytic properties, such as the proton-donating properties, of the medium were termed secondary solvent effects. Evidence was adduced for both types of effects in oxotropic rearrangements.

It was shown that in the rearrangement of propenylethynylcarbinol in aqueous ethanol the decrease in rate constant with increasing concentration of organic solvent (c_s) could be expressed in the form $\log k = mD + n$ where D is the dielectric constant, and m and n are constants and $c_s \leq 80\%$. This was interpreted mainly as a secondary solvent effect, the decrease in dielectric constant resulting in a decrease in the proton-donating properties of the medium. It was further shown that on this basis a correction could be applied to the Arrhenius energy of activation to allow for the change in dielectric constant of the medium with temperature, the isodielectric energy of activation being given by $E_{[D]} = E_{Arr.} + RT_1 T_2 mb$ where T_1 , T_2 are the limits of the temperature range investigated, and b is a constant defined by $D = a + bt$, t being the temperature in °C. Whereas $E_{Arr.}$ varied considerably with solvent composition, $E_{[D]}$ was independent of it within the limits of experimental error. Similar observations were made (Part V, *loc. cit.*) with the rearrangement of phenylpropenylcarbinol in aqueous ethanol and aqueous dioxan, though $E_{[D]}$ in the latter case was ca. 4 kg.-cals./mol. lower than in the former, the difference being ascribed to a primary solvent effect, namely, increased solvation of the carbinol group by the dioxan.

The independence of $E_{[D]}$ of medium composition thus applies only as long as there is no appreciable change in solvating properties. Independent evidence for the occurrence of primary solvent effects was provided by the small but definite variations in the slope of the $\log k - c_A$, and $\log k - c_s$ plots with different substituted ethylenic and acetylenic carbinols (Parts III and IV, *J.*, 1946, 122, 128). These variations are presumably due to small differences in the extent of solvation of the carbinols by the solvent. If secondary solvent effects alone came into play, these slopes should be the same for different compounds undergoing the same reaction by

identical mechanisms. The data now obtained for substituted phenylpropenylcarbinols also indicate the occurrence of both primary and secondary solvent effects.

Specific k and relative rate constants, dielectric constant effects (expressed as m , the slope of the rate constant-dielectric constant plot), Arrhenius and isodielectric energies of activation, and reaction constants A (defined by $k/c_A = Ae^{-E_{(D)}/RT}$)[†] are given in Table IV; m varies somewhat for different carbinols, being lower when $R = \text{Me}$ or MeO , and higher when $R = \text{Halogen}$, as compared with $R = \text{H}$ (see I). But whereas values of $E_{\text{Arr.}}$ for any one carbinol are higher by 2–3 kg.-cals./mol. for 60% as compared with 40% aqueous dioxan, the corresponding values of $E_{(D)}$ differ by not more than 0.4 kg.-cal./mol. in seven cases, and by 0.9 kg.-cal./mol. when $R = p\text{-MeO}$. Within the range examined, the energy of activation is thus again independent, or nearly so, of the composition and hence of the dielectric constant of the medium, when allowance is made for the different temperature coefficients of the dielectric constants of different media.

TABLE IV.

Specific and relative rate constants, Arrhenius parameters, and isodielectric energies of activation for the rearrangement of $\text{C}_6\text{H}_4\text{R}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{CHMe}$ in aqueous dioxan (percentage of dioxan given in parentheses). r = Rate constant relative to phenylpropenylcarbinol ($R = \text{H}$).

R.	k/c_A for 0.001M-HCl, (60%), 30.0°.	m .	$E_{\text{Arr.}}$ (40%).	$E_{\text{Arr.}}$ (60%).	$E_{(D)}$ (40%).	$E_{(D)}$ (60%).	$\log A$ (60%).	r .	$10^3 K^*$
H	1.79	0.033	18.2	19.5	20.7	20.6	13.3	1	6.3
<i>o</i> -Me	3.59	0.032	18.2	19.5	20.7	20.6	13.6	2.0	12.3
<i>m</i> -Me	2.17	0.028	18.8	20.4	21.0	21.4	14.0	1.2	5.4
<i>p</i> -Me	16.1	0.033	18.1	19.6	20.7	20.7	14.4	9.0	4.2
<i>p</i> -F	1.50	0.036	17.7	19.4	20.5	20.7	13.4	0.84	7.2
<i>p</i> -Cl	0.434	0.036	19.6	20.3	22.2	21.6	13.4	0.24	10.6
<i>p</i> -Br	0.340	0.034	19.3	20.4	21.9	21.6	13.3	0.19	10.7
<i>p</i> -MeO	189	0.029	15.7	17.9	18.0	18.9	14.1	105	3.4

* Dissociation constants of $\text{C}_6\text{H}_4\text{R}\cdot\text{CO}_2\text{H}$ in water at 25° (Dippy, *Chem. Reviews*, 1939, **25**, 206).

Regarding the correlation of rate constants, energies of activation, and reaction constants with substituents, this may be summarised as follows: (i) The rate constants are increased by methyl substituents in the order $\text{H} < m\text{-Me} < o\text{-Me} < p\text{-Me}$, strongly increased by a *p*-MeO group, and decreased by *p*-halogen substituents in the order $\text{H} > p\text{-F} > p\text{-Cl} > p\text{-Br}$. (ii) Isodielectric energies of activation are constant at 20.6 (± 0.1) kg.-cals./mol. when $R = \text{H}$, *o*-Me, *p*-Me or *p*-F, slightly increased (by 0.3–1.5 kg.-cals./mol.) when $R = m\text{-Me}$, *p*-Cl or *p*-Br and decreased (by 2 kg.-cals./mol.) when $R = p\text{-MeO}$. (iii) Reaction constants (A) are constant at 13.4 (± 0.1) sec.⁻¹ when $R = \text{H}$ or Halogen, and slightly increased by $R = \text{Me}$ in the order $o\text{-Me} < m\text{-Me} < p\text{-Me}$, and by $R = \text{MeO}$.

In aqueous-ethanolic media, the first-order law is obeyed when $R = \text{H}$, *p*-Me, *p*-F, or *p*-MeO, but with the *p*-Cl and *p*-Br substituted carbinols the first-order rate constants fall as the reaction proceeds (see Experimental) in a manner reminiscent of that previously observed with phenylvinylcarbinol (Part V, *loc. cit.*) and shown there to be due to etherification occurring before, as well as simultaneously with, rearrangement.

EXPERIMENTAL.

Materials.—The preparation and properties of the phenylpropenylcarbinols and of their styryl isomers are described in the preceding paper. Dioxan was purified by the method of Hesse and Frahm (*Ber.*, 1938, **71**, 2629).

Kinetic Measurements.—The technique was the same as described in Part V (*loc. cit.*) and preceding papers. Initial and end values are given as $E_{1\%}^{\text{inc.}}$ [$= \log (I_0/I)/cl$, where I_0 = intensity of incident light, I = intensity of transmitted light, c = concentration in % w/v, l = cell length in cm.] (Table V).

Typical runs for each carbinol, in aqueous dioxan and ethanolic media, are reproduced below. The first-order rate constants (k) are calculated by $k = (2.3/z) \log [(a - x_0)/(a - x)]$, where z = time in

* Since k is not directly proportional to c_A when $c_A > 0.1\text{M}$ in the present reaction, the specific rate constants (k/c_A) are not equal to k when $c_A = 1\text{M}$. Nevertheless for purposes of comparison of different series, specific rate constants are obviously preferable to k 's at an arbitrary acid concentration. The values given in Parts III and IV (J., 1946, 122, 128, Tables III, cols. 1) for the rearrangement of acetylenyl- and vinyl-carbinols should be divided by 10^3 to convert them into k/c_A . Although these measurements refer to 60% aqueous ethanol media, the specific constants are then comparable to the present ones, since rate constants in 60% dioxan and ethanol are not appreciably different (see below and Part V, *loc. cit.*).

† In a catalysed reaction, A depends on the catalyst concentration, and the choice of the latter is arbitrary. For purposes of standardisation it appears preferable to base A on the specific rate constant k/c_A . The values given in Parts III and IV (*loc. cit.*, cols. 3) should accordingly be increased by 1.0.

Time (mins.)	0	1	2	3	4	5	120
$E_{\text{cm.}}^{1\%}$ (2480 Å.)	90	195	290	390	470	525	1200
$10^6 k$ (min. ⁻¹)	—	1020	1020	1080	1080	1030	— (Mean) 1050

(iii) R = *p*-Cl. $c_{\text{ROH}} = 0.1$, $c_A = 0.02$.

Time (mins.)	0	6	12	15	18	21	24	27	600
$E_{1\text{cm.}}^{1\%}$ (2560 Å.)	130	340	470	530	570	600	625	655	1100
$10^4 k$ (min. ⁻¹)	450 *	406	359	354	335	308	297	288	—

(iv) R = *p*-Br. $c_{\text{ROH}} = 0.2$, $c_A = 0.02$.

Time (mins.)	0	5	10	15	20	25	30	1440
$E_{1\text{cm.}}^{1\%}$ (2580 Å.)	80	220	350	450	525	590	630	990
$10^4 k$ (min. ⁻¹)	420 *	400	385	357	376	340	320	—

(v) R = *p*-MeO. $c_{\text{ROH}} = 0.2$, $c_A = 0.001$, $t = 30.0^\circ$.

Time (mins.)	0	2	3	4	5	6	7	8	120
$E_{1\text{cm.}}^{1\%}$ (2610 Å.)	120	360	475	550	630	700	780	840	1300
$10^4 k$ (min. ⁻¹)	—	1140	1180	1130	1120	1130	1170	1180	(Mean) 1150

* Extrapolated.

DISCUSSION.

With regard to the reaction mechanism, this is clearly the same throughout the series, since such characteristics as reaction order, dependence of the rate constants on carbinol, acid, and solvent concentrations, and the independence of the isodielectric energies of activation of solvent composition are the same in each case. The interpretation of substituent effects can therefore be based on the mechanism already outlined and discussed for the rearrangement of the parent compound, phenylpropenylcarbinol (Part V, *loc. cit.*)*

Table IV shows that the differences in the rate constants are due to variations in both the energy of activation and the non-exponential factor A of the Arrhenius equation. Except with the *p*-methoxy-compound, however, where $E_{(p)}$ is distinctly lower, while A is only slightly higher than for phenylpropenylcarbinol, these variations are only small and mostly entail differences of the same order of magnitude as the experimental error. In view of this fact, only tentative conclusions can be based on such regularities as can be discerned, and it will be preferable at this stage of the investigation to limit the discussion mainly to a consideration of the changes in the relative rate constants brought about by substituents.

Ingold's classification (*J.*, 1933, 1120; *Chem. Reviews*, 1934, 15, 233; see also Baker, "Tautomerism," Routledge, London, 1934; Remick, "Electronic Interpretation of Organic Chemistry," Wiley, New York, 1943) of substituent effects, which is now generally accepted, recognises two principal types: (i) the general inductive (I) and (ii) the tautomeric effect (T). The former depends on the capacity of the atom or group to attract or repel electrons and is mainly electrostatic in origin, I being negative with respect to hydrogen (electron-attraction) when the electronegativity of the substituent is greater than that of hydrogen, *i.e.*, when $x_R > x_H$, and positive (electron-repulsion) when $x_R < x_H$. The tautomeric effect, on the other hand, depends on the capacity of a substituent to share an additional electron pair, *i.e.*, on its capacity for covalency increase or decrease, and on its capacity to favour resonance forms of the type $R^+ \equiv A - B^-$ or $R^- \equiv A - B^+$ in systems classically represented by $R - A \equiv B$. In the case of alkyl groups, the central atom carries no unshared electron-pair and their tautomeric effect must be ascribed to no-bond resonance in the C—H links, *i.e.*, contributions from $H^+C \equiv C - C^-$ to systems classically represented by $H - C - C \equiv C$ (Baker, *J.*, 1939, 1150).

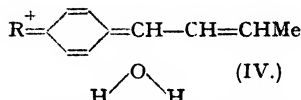
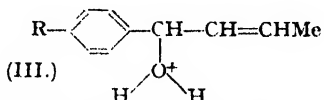
In the mechanism proposed for the present reaction, both steps require electron accession at the point of reaction and k should therefore be increased by $+I$ and $+T$ effects and retarded by $-I$ effects. This has been shown to be the case for alkyl and alkenyl substituents attached to the aliphatic part of the molecule (Parts III, IV, and V, *loc. cit.*). Similarly, the present data for the three tolylpropenylcarbinols are in accordance with expectations, the accelerating effect of the methyl substituent being least in the *m*-position ($+I$ effect only) and larger in the *o*- and *p*-positions ($+I$ and $+T$ effects). The fact that the increase in k due to an *o*-methyl group is less than that of a *p*-methyl group, although the $+I$ and probably the $+T$ effect should be greater for the former, provides yet another example of the well-known "ortho"-effect: the decrease in planarity due to the ortho-substituent inhibits the transmission of the T effect. However, even the "true" $+T$ effect is unlikely to be much larger in the *ortho*-

* The kinetic criterion given in Part V (*loc. cit.*, p. 403, lines 42 and 43) is erroneous. A valid criterion for the distinction between $ROH + H^+ \xrightarrow{\text{slow}} ROH_2^+ \xrightarrow{\text{fast}} R'OH_2^+$, and $ROH + H^+ \xrightarrow{\text{fast}} ROH_2^+ \xrightarrow{\text{slow}} R'OH_2^+$ was correctly stated in Part II (*J.*, 1944, 443) and depends on the linear relation between $\log k$ and the acidity function H_0 , rather than between $\log k$ and c_A .

than in the *para*-position, and the roughly tenfold increase in k due to a methyl substituent in the phenyl ring may be compared with its much larger effect when attached to the ethylenic double bond. Thus phenylpropenylcarbinol rearranges about 500 times faster than phenylvinylcarbinol under identical conditions (Part V, *loc. cit.*). This large difference is to be ascribed to the fact that the double-bond electron-pair moves towards the (electron-repelling) methyl substituent in one case, and away from it in the other, as well as possibly to a greater polarisability (allowing a readier transmission of the $+T$ effect) of the ethylenic double bond as compared with the aromatic system.

A p -MeO group also has the expected accelerating influence owing to its large $+T$ effect, but with the halogeno-carbinols the results are not entirely those to be anticipated from *a priori* considerations. The $-I$ effect should lead to reduction in the rate constant and to the sequence $F < Cl < Br < H$, since the electronegativity differences are in this order (F 4.0, Cl 3.0, Br 2.8, H 2.1; Pauling, "Nature of the Chemical Bond," Cornell, 1940). The $+T$ effect should counteract this diminution, but since it should be largest for Br and least for F and since it is smaller than the $-I$ effect, the actual sequence $F < Cl < Br < H$ should remain unaltered. The observed sequence is the reverse, *i.e.*, $Br < Cl < F < H$, which means that the $+T$ effects vary in the order $F > Cl > Br$ and not $F < Cl < Br$. This is unexpected, since the control of the nucleus over the valency electrons should decrease, and the capacity for covalency increase on ascending a group of the periodic table. Similar results indicating a reversed sequence of the tautomeric effects in the halogens have been observed in several other cases (Shopee, *J.*, 1933, 696; Baddeley, Bennett, *et al.*, *J.*, 1933, 261, 1112; 1935, 1827). It must be emphasised, however, that this interpretation is based on the tacit assumption that the rate constants as such, rather than the energies of activation and reaction constants separately, represent an adequate and additive measure of I and T effects.

It is noteworthy that the p -methoxyl substituent, which is the only one producing a large (*i.e.*, over 100-fold) change in rate, results in pronounced lowering of the energy of activation ($\Delta E_{[D]} = ca. 2$ kg.-cals.), just as the 500-fold increase in rate due to the β -methyl group in phenylpropenyl- as compared with phenylvinyl-carbinol is accompanied by a large decrease in $E_{[D]}$ of *ca.* 5 kg.-cals./mol. (Part V, *loc. cit.*). The data for the rearrangements of acetylenyl- and vinyl-carbinols (Parts III and IV, *loc. cit.*) also bear out that, on the whole, an increase in rate is accompanied by a decrease in the energy of activation,* and that large changes in rate depend on large changes in the energy of activation rather than $\log A$. This is readily interpreted as indicating that although the effect of substituents is exerted to a small extent by changes in the equilibrium constant of the preceding proton-transfer equilibrium, $ROH + H^+ \rightleftharpoons ROH_2^+$, their main effect lies in altering the energy requirements of the rate-determining isomerisation $ROH_2^+ \rightarrow R'OH_2^+$. An electron-repelling substituent increases the electron-density at the point of reaction, through increased contribution from resonance forms such as (IV), thereby partly neutralises the positive charge at the reaction centre, and decreases the energy of separation of the carbonium ion and the dipolar water molecule. The existence of extended conjugation in the resonance form of the oxonium ions of phenylpropenylcarbinols may also explain why substituents exerting $+T$ effects enhance the tendency for equilibrium formation: rearrangement to the styryl isomer results in increased conjugation, and hence, lowering in potential energy, only in the "ordinary" form (III), but not in the resonance form (IV).

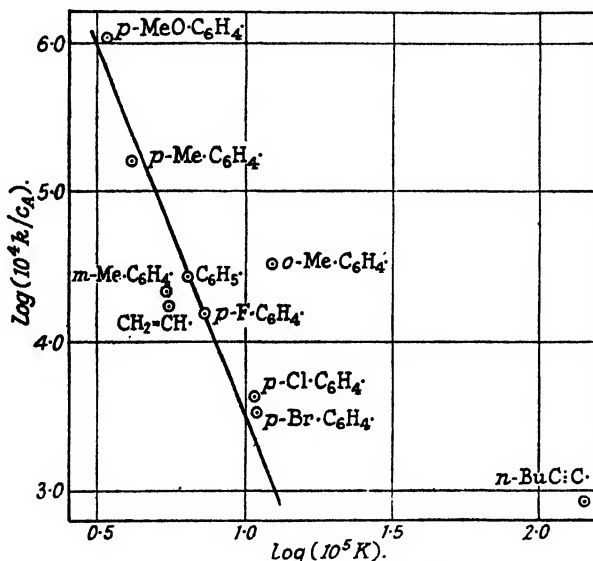


From a qualitative study of the rearrangement-acetylation of p -methylstyrylphenyl- and p -chlorostyrylphenyl-carbinols, and of p -tolyl- and p -chlorophenyl-vinylcarbinols, Burton and Ingold (*J.*, 1928, 904) and Burton (*J.*, 1928, 1650) concluded that the reaction is facilitated in the order $p\text{-Cl-C}_6\text{H}_4 > p\text{-Me-C}_6\text{H}_4 > \text{Ph}$, and that this was the expected order of reactivity. However, since the mechanism postulated by these authors, though different from the one adopted here, also requires electron-accession at the point of reaction, and since the overall electron-attracting effect of the halogens ($-I > +T$) is well known from aromatic substitution and other reactivity

* This conclusion was not drawn in the two papers referred to and only holds if the uncertain values of E (marked ~) for a few of the carbinols are disregarded. It now appears probable that the possibility, already envisaged in Part III, of equilibria being set up in these cases does apply, and that the E values derived from the temperature coefficients of the over-all rate constants do not represent real energies of activation in these cases.

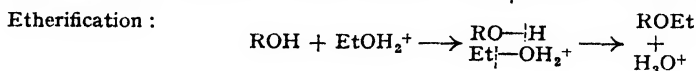
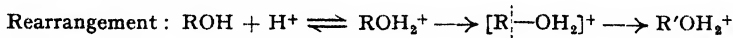
data, this expectation is clearly incorrect, and the expected sequence should be $\text{Me}\cdot\text{C}_6\text{H}_4 > \text{Ph} > \text{Cl}\cdot\text{C}_6\text{H}_4$ as confirmed by the present data. Moreover, inspection of the experimental results of Burton and Ingold also appears to indicate this sequence of reactivity and not the one deduced by their authors. Thus phenylvinyl- and *m*- and *p*-tolylvinyl-carbinols are stated to be converted completely into the corresponding styrylcarbiny acetates by treatment with boiling acetic anhydride for six hours, while identical treatment of *p*-chlorophenylcarbinol is stated to lead to a mixture containing only *ca.* 70% of the rearranged acetate. It may well be that the probable equilibrium formation in the rearrangements of *p*-chloro- and *p*-bromo-phenylpropenylcarbinols (see above) is enhanced in the less reactive phenylvinyl homologues.

The electron-attracting effect of the chloro- and bromo-substituents is also well illustrated by the fact that they appear to facilitate ether formation in ethanolic acid solution sufficiently for it to occur before rearrangement; with a fluoro-substituent the effect is not sufficiently great to lead to a falling first-order constant. Unlike the rearrangement reaction, which depends on the fission of the carbon-oxygen bond and electron accession at the point of reaction,



k = Rate constant of $\text{R}\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{CHMe}$.
 K = Dissociation constant of $\text{R}\cdot\text{CO}_2\text{H}$ (see Table IV).

ether formation probably depends on the bimolecular fission of the hydrogen-oxygen bond, *i.e.*, on electron recession at the point of reaction.



The ease of etherification of phenylvinylcarbinol (Part V, *loc. cit.*) is similarly to be ascribed to the strong electron-attraction ($-I$ effect) of the free vinyl group; in phenylpropenylcarbinol this is counteracted by the electron-repelling ($+I$, $+T$) effects of the β -methyl group and no etherification occurs prior to rearrangement.

Some correlation might again be expected between the specific rate constants of the carbinols and the dissociation constants (K) of the corresponding benzoic acids (cf. Parts IV and V, *loc. cit.*). The plot of $\log k/c_A$ against $\log K$ does in fact approximate to a straight line (Table IV; Fig.), except when $\text{R} = o\text{-Me}$. This is another instance of the "ortho"-effect (cf. Hammett, "Physical Organic Chemistry," McGraw Hill, New York, 1941). The point for vinylpropenylcarbinol (Part IV, *loc. cit.*) also falls on the straight line, but the points for ethynylpropenyl- and hexynylpropenyl-carbinols do not, and thus both the acetylenic groups and not the ethynyl group only, as previously thought, behave differently in this respect from the other groups so far examined.

The authors of this and the preceding paper are indebted to Professor Sir Ian Heilbron, D.S.O., F.R.S., for his interest, to the Rockefeller Foundation for financial assistance, and to the Chemical Society for a grant.

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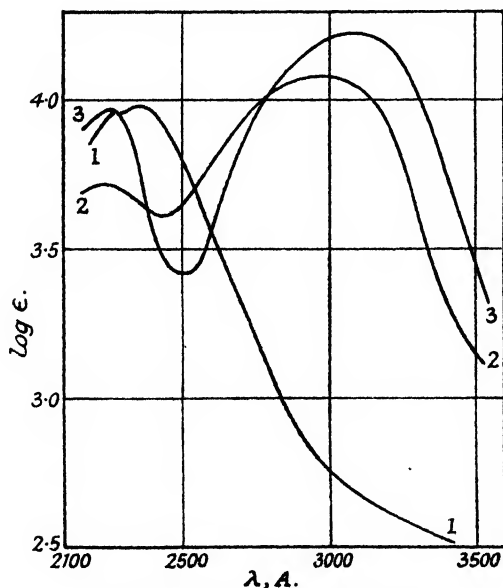
[Received, November 26th, 1946.]

207. Studies in Light Absorption. Part IV. Nitro-olefins.

By ERNEST A. BRAUDE, E. R. H. JONES, and G. G. ROSE.

The ultra-violet light absorption of a number of compounds containing the conjugated chromophoric systems $C:C\cdot X$, $C:C\cdot C:C\cdot X$, and $Ph\cdot C:C\cdot X$ where $X = NO_2$ has been examined, and found to be similar to that of the corresponding systems where $X = C:C$, $C:N$, $C:O$, etc.

It is well known that chromophoric systems of the type $C:C\cdot X$, where X is a covalently unsaturated group such as $C:C$, $C:N$, or $C:O$, all exhibit selective high-intensity absorption in the 2200 Å. region (cf. Braude, *Ann. Reports*, 1945, 42, 105). The spectral properties of nitro-olefins ($X = NO_2$) have not hitherto been recorded. Since the conjugating properties of the nitro-group when attached to a phenyl group are known to resemble those of other covalently unsaturated groups (*e.g.*, nitrobenzene, styrene, benzaldehyde, and its *N*-methylimide all



Light absorption (in ethanol) of :

1. $CHMe:CH\cdot NO_2$. 2. $CHMe:CH\cdot CH:CH\cdot NO_2$. 3. $Ph\cdot CH:CH\cdot NO_2$.

exhibit similar ultra-violet light absorption due to the chromophoric system $Ph\cdot X$), the nitro-olefin system $C:C\cdot N\begin{smallmatrix} O \\ // \\ O \end{smallmatrix}$ would also be expected to absorb intensely in the 2200 Å. region. Data for a number of representative compounds (Table; Fig.) show that this expectation is fulfilled, but the maxima are situated at somewhat longer wave-lengths than in the formally related $C:C\cdot C:O$ and $C:C\cdot C\begin{smallmatrix} O \\ // \\ OH \end{smallmatrix}$ systems.

Although an isolated nitro-group, just as a carbonyl group, gives rise to a low-intensity band near 2700 Å. (Zelinsky and Rosanoff, *Z. physikal. Chem.*, 1912, 78, 629; Goodeve, *Trans. Faraday Soc.*, 1934, 30, 504; Kortüm, *Z. physikal. Chem.*, 1939, B, 43, 271), nitro-olefins exhibit no band corresponding to the displaced carbonyl band at 3200 Å. shown by $\alpha\beta$ -ethylenic carbonyl compounds. The solvent effects in the two systems are similar, λ_{max} (ethanol) being higher than λ_{max} (*n*-hexane) by an average of *ca.* 100 Å. with the nitro-olefins,

and by *ca.* 70 Å. with $\alpha\beta$ -ethylenic carbonyl compounds (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72; Evans and Gillam, *J.*, 1945, 432). On the other hand, in the case of the nitro-olefins, vibrational structure appears to be more pronounced in ethanol than in hexane, which is unexpected since the former is generally the more highly solvating solvent.

Lengthening of the conjugated chain as in the α -nitrobutadiene and β -nitrostyrene systems, *i.e.*, $C_6H_5C_4H_3NO_2$ and $PhC_4H_3NO_2$, respectively, results in the expected increase in λ_{max} , and the positions of the long wave-length bands are again 200–300 Å. higher than those of the corresponding bands shown by the $C_6H_5C_3H_3O$ and PhC_3H_3O systems. The persistence of shorter wave-length bands, probably to be ascribed to the partial chromophore $C_6H_5C_2H_3O$, is peculiar to the nitro-compounds.

The effects of auxochromic substituents are similar to those observed in other systems (cf. Part III, *J.*, 1946, 948); λ_{max} is increased by alkyl and halogen substituents attached to the $\alpha\beta$ -ethylenic bond, thus, $\Delta\lambda_{Me} = ca.$ 100 Å., and $\Delta\lambda_{Br} = ca.$ 300 Å. in the nitro-ethylenes. In the nitrostyrene system the effects are smaller or negative, thus, for β -substituents $\Delta\lambda_{Me} = -50$ Å., $\Delta\lambda_{Cl} = 100$ Å., and $\Delta\lambda_{Br} = 150$ Å.

Ultra-violet light absorption of nitro-olefins in ethanol and n-hexane.

	Ethanol.		n-Hexane.	
	λ_{max} , Å.	ϵ_{max} .	λ_{max} , Å.	ϵ_{max} .
$CH_2=CMe\cdot NO_2$	2250	3,300	*	*
$CHMe:CH\cdot NO_2$	2290	9,400	2290	8,700
	2350	9,700		
$CHMe:CMe\cdot NO_2$	2340	5,600	2350	6,100
	2420	5,800		
	2500	5,600		
$CMe_2:CH\cdot NO_2$	2450	8,600	2350	10,000
	2510	8,600		
$CHPr^\beta:CMe\cdot NO_2$	2420	6,000	2340	5,400
	2510	6,200	2420	5,600
	2580	6,000		
$CHMe:CBr\cdot NO_2$	2250	4,000	*	*
	2690	4,800		
$CHMe:CH:CH:CH\cdot NO_2$	2260	5,500	*	*
	2980	12,000		
$CHPh:CH\cdot NO_2$	2270	9,500	2230	10,300
	3090	16,500	2290	9,700
			2990	17,800
$CHPh:CMe\cdot NO_2$	2260	10,300	2230	9,500
	3050	12,400	2930	11,400
$CHPh:C\sim Cl\cdot NO_2$	2260	10,600	*	*
	3200	13,600		
$CHPh:CBr\cdot NO_2$	2260	8,700	*	*
	3240	12,000		

* Not determined.

EXPERIMENTAL.

For the technique of the light absorption measurements, see Part I (*J.*, 1945, 490). The compounds examined had the following physical constants: 2-Nitroprop-1-ene, b. p. 68–70°/144 mm., n_D^{20} 1.4309; 1-nitroprop-1-ene, b. p. 45°/1.5 mm., n_D^{20} 1.4663 (Schmidt and Rutz, *Ber.*, 1928, **61**, 2142); 2-nitrobut-2-ene, b. p. 47–50°/9 mm., n_D^{20} 1.4616; 1-nitro-2-methylprop-1-ene, b. p. 48–49°/9.5 mm., n_D^{20} 1.4723 (Haitinger, *Annalen*, 1878, **193**, 368; *Monatsh.*, 1881, **2**, 286); 2-nitro-4-methylpent-2-ene, b. p. 67°/10 mm., n_D^{20} 1.4579; 1-bromo-1-nitroprop-1-ene, b. p. 59–60°/11 mm., n_D^{20} 1.5121; 1-nitropenta-1:3-diene, b. p. 78–79°/2.5 mm., n_D^{20} 1.5543; β -nitrostyrene, m. p. 57–58° (Worall, *Org. Synth.*, Coll. Vol. I, p. 413); β -nitro- β -methylstyrene, m. p. 64°; β -chloro- β -nitrostyrene, m. p. 48° (Priests, *Annalen*, 1884, **225**, 321); β -bromo- β -nitrostyrene, m. p. 66° (Worall, *J. Amer. Chem. Soc.*, 1921, **43**, 919). They were prepared either according to the methods given in the references cited, or by methods which will be described in a separate publication. We are indebted to Drs. R. L. Heath and H. A. Piggott of I.C.I. Ltd., Dyestuffs Division, for a sample of 2-nitro-4-methylpent-2-ene.

The authors thank Professor Sir Ian Heilbron, D.S.O., F.R.S., for his interest, and the Rockefeller Foundation for financial assistance.

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[Received, November 26th, 1946].

208. Syntheses in the Thiopyran Series. Part I. Tetrahydro-derivatives.

By RALPH F. NAYLOR.

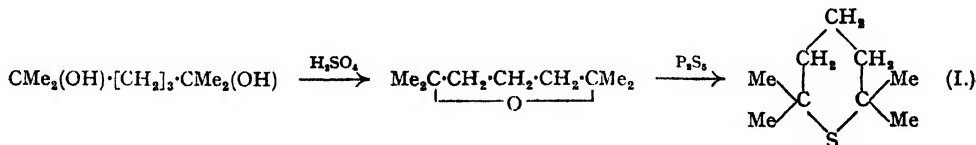
Reaction of a 1 : 5-dibromo-compound with sodium sulphide is not applicable to the synthesis of those members of the tetrahydrothiopyran series which contain tertiary carbon atoms in the 2- and the 6-position. In such cases it is possible to achieve the synthesis by cyclisation of the appropriate 2 : 6-diol to give the corresponding tetrahydropyran, followed by reaction of the latter with phosphorus pentasulphide. By this method 2 : 2 : 6 : 6-tetramethyl- and 2 : 2 : 6-trimethyl-6-ethyl-tetrahydrothiopyran have been prepared.

RECORDED investigation of compounds of the tetrahydrothiopyran series has been limited to two of the simplest members, pentamethylene sulphide and 1-methylpentamethylene sulphide, which have been readily obtained by reaction of the appropriate dihalide with sodium sulphide (Clarke, *J.*, 1912, 101, 1805; v. Braun, *Chem. Zentr.*, 1909, II, 1994; Grischkewitsch-Trochimowski, *Chem. Zentr.*, 1923, I, 1503). A few of the corresponding saturated thiopyrones have been prepared either by addition of hydrogen sulphide to a keto-diene or by cyclisation of a suitable aliphatic sulphide (Arndt and co-workers, *Ber.*, 1925, 58, 1633; 1930, 63, 313, 2393; Bennett and Scoriah, *J.*, 1927, 194), but otherwise no work has been recorded on this class of compound.

Although pentamethylene bromide reacts fairly readily with sodium sulphide, the yields of tetrahydrothiopyran are less than those reported to be obtainable with the chloride. This is in accord with the work of Bost and Conn (*Oil and Gas J.*, 1933, 32, No. 3, 17), who obtained only 30% of 2-methyltetrahydrothiopyran from 1 : 5-dibromohexane. In the present work it was desired to prepare tetra-substituted 2 : 6-derivatives, and to this end 2 : 6-dibromo-2 : 6-dimethylheptane was synthesised from ethyl glutarate :



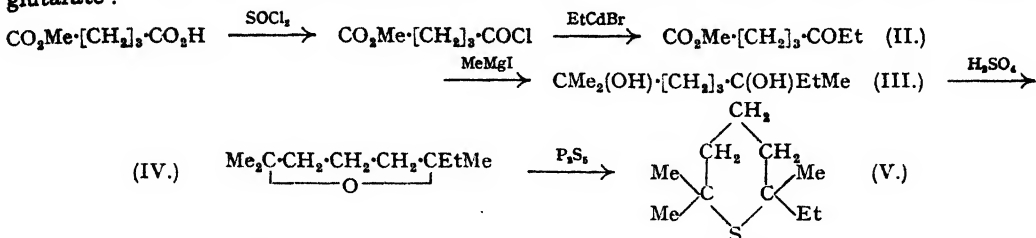
On trial, however, the lability of the bromine attached to the tertiary carbon atoms proved to be such that reaction of the bromide with sodium sulphide in alcoholic solution resulted only in the replacement of Br by OEt, and the corresponding reaction without a solvent resulted in loss of hydrogen bromide with formation of monobromodimethylheptenes and geraniolene ($\text{C}_{10}\text{H}_{18}$). This failure necessitated recourse to the less attractive method presented by conversion of a suitable pyran into the sulphur analogue. 2 : 6-Dimethylheptane-2 : 6-diol had already been observed to cyclise when it was heated in the presence of mineral acid, so giving 2 : 2 : 6 : 6-tetramethyltetrahydropyran* (Bruylants, *Rec. Trav. chim.*, 1910, 29, 130). This pyran was found to give a small yield of the desired 2 : 2 : 6 : 6-tetramethyltetrahydrothiopyran (I) when it was heated with phosphorus pentasulphide. The reaction, however, was complex, giving accompanying (resinous) products, which were not investigated.



Synthesis of unsymmetrical members of the thiopyran series presented greater difficulty, but since the essential oxide-sulphide conversion must remain the same in view of the presence of tertiary groupings, the only concern was the building up of the required carbon

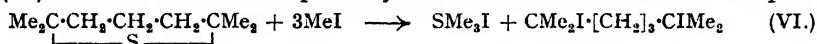
* It is to be noted that no isomerisation involving shift of the -OH groups, such as has been observed by Franke and Gomolka (*Monatsh.*, 1929, 56, 331) in the case of $\alpha\omega$ -diols, $\text{CH}_3(\text{OH}) \cdot [\text{CH}_2]_n \cdot \text{CH}_2\text{OH}$, is possible in this dehydration, owing to the tertiary nature of the hydroxylated carbon atom : if water is eliminated with the formation of a double bond, the Markownikow rule will ensure that any re-addition of water will give the original alcohol $[\text{CH}_2 \cdot \text{C}(\text{OH})\text{Me}]_n \xrightarrow{-\text{H}_2\text{O}} \text{CH} : \text{CMe}_2 \xrightarrow{+\text{H}_2\text{O}} \text{CH}_2 \cdot \text{C}(\text{OH})\text{Me}_2$. In consequence only six-membered rings can arise. The six-membered nature of the subsequent thiopyran rings has been confirmed by the identity of their infra-red spectra with those of necessarily six-membered cyclic sulphides derived from hydrogen sulphide addition to di-isoprenes (Sutherland and Sheppard, in the press; Naylor, in the press).

framework. This was accomplished by the following steps, starting from methyl hydrogen glutarate :



Clutterbuck and Raper (*Biochem. J.*, 1925, 19, 393) report the preparation of methyl δ -ketoheptanoate (II) by reaction of ethylzinc iodide with the half-ester half-acid chloride of glutaric acid, but do not record yield. In the present work the zinc alkyl was replaced by ethylcadmium bromide, which reacted with the acid chloride group while leaving the ester group untouched, and a satisfactory yield (58%) of the δ -keto-ester (II) was isolated. By reaction with 3 mols. of methylmagnesium iodide (II) was converted into 2 : 6-dimethyloctane-2 : 6-diol (III), which condensed in the presence of warm dilute acid to 2 : 2 : 6-trimethyl-6-ethyl-tetrahydrothiopyran (IV). The final stage was treatment of (IV) with phosphorus pentasulphide to yield 2 : 2 : 6-trimethyl-6-ethyltetrahydrothiopyran (V).

The tetrahydrothiopyrans are quite stable towards acids and alkalis, but oxidise slowly in air. They unite with methyl iodide in the cold, but the resulting methiodides often separate as oils, which are difficult to crystallise. The rings of the sulphides (I) and (V) open when the compounds are heated with methyl iodide, the sulphur being removed as trimethylsulphonium iodide. This behaviour is in contrast to the stability of cyclic sulphides, containing primary α -carbon atoms, and is interesting in comparison with the formation of trimethylsulphonium iodide by the action of methyl iodide at 15° on compounds containing the diallylic sulphide grouping, $\cdot\text{CH}_2\cdot\text{CH}\cdot\text{CH}_2\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}\cdot\text{CH}_2\cdot$ (Selker and Kemp, *Ind. Eng. Chem.*, 1944, 36, 17). The di-iodide (VI) was not isolated and is probably too unstable to be obtained in the pure state.



EXPERIMENTAL.

(Microanalyses were carried out by Dr. W. T. Chambers, Miss H. Rhodes, and Miss E. Farquhar.)

Pentamethylene Sulphide.—Pentamethylene bromide was prepared from piperidine by the method described in *Organic Syntheses*, Coll. Vol. I, pp. 93, 419. A solution of the bromide (40 g.) and anhydrous sodium sulphide (50 g.) in ethanol (250 ml.) was refluxed for 3 hours. After addition of excess of water the product was extracted with ether and twice distilled. Pentamethylene sulphide (6 g., 34%) was obtained as a liquid, b. p. 140°/756 mm., n_D^{20} 1.5055 (Found : C, 59.0; H, 10.0; S, 31.3. Calc. for $\text{C}_5\text{H}_{10}\text{S}$: C, 58.9; H, 9.8; S, 31.4%).

Synthesis of 2 : 2 : 6-Tetramethyltetrahydrothiopyran (I).—(a) *Action of sodium sulphide on 2 : 6-dibromo-2 : 6-dimethylheptane.* Magnesium (4.5 g.) under ether was dissolved in a solution of methyl iodide (270 g.) in ether (350 ml.), and to the cooled solution of methylmagnesium iodide was introduced with stirring ethyl glutarate (64 g.) in ether (75 ml.). When the reaction moderated, the solution was refluxed for 1 hour, left overnight, and then poured slowly into aqueous ammonium chloride (200 g. in 700 ml.) containing crushed ice (2000 g.). 2 : 6-Dimethylheptane-2 : 6-diol was extracted with ether both before and after concentration of the aqueous solution, and was obtained from this extract as the monohydrate (30 g.) which was distilled at 85°/1 mm. to give the anhydrous alcohol (21 g.), m. p. 76°. Dry hydrogen bromide was bubbled through an ethereal solution of the alcohol at 0°; after neutralisation of excess acid with sodium hydrogen carbonate, 2 : 6-dibromo-2 : 6-dimethylheptane crystallised out in white needles, m. p. 34° (Found : C, 38.1; H, 6.4. Calc. for $\text{C}_9\text{H}_{18}\text{Br}_2$: C, 37.8; H, 6.3%). The dibromide lost hydrogen bromide very readily, even at room temperature, under reduced pressure. A solution of sodium sulphide (20 g.) and the dibromide (5 g.) in ethanol (50 ml.) was refluxed for 2½ hours, then diluted with water and ether extracted. The extract contained geraniolene (b. p. 40°/13 mm.) and impure 2 : 6-diethoxy-2 : 6-dimethylheptane (b. p. 70°/13 mm.; n_D^{18} 1.4452), but no sulphur-containing compounds. By heating together the dibromide (5 g.) and dry powdered sodium sulphide (25 g.) for 5 hours at 100–110° was obtained a mixture of geraniolene (b. p. 38°/12 mm.), impure bromo-2 : 6-dimethylheptane (b. p. ca. 50°/1 mm.; n_D^{18} 1.4748), and unchanged dibromide (b. p. 72°/1 mm.; m. p. 24°).

(b) *Action of phosphorus pentasulphide on 2 : 2 : 6-tetramethyltetrahydrothiopyran.* 2 : 6-Dimethylheptane-2 : 6-diol (15 g.), prepared as above, was shaken with 2N-sulphuric acid at 100° for 3 hours; the product contained unchanged diol, geraniolene, and 2 : 2 : 6-tetramethyltetrahydrothiopyran, b. p. 48°/1 mm. The last (7 g.) was sealed with phosphorus pentasulphide (24 g.) in a nitrogen-filled Carius tube, and heated for 6 hours at 110–120°. The product was extracted with aqueous alkali, dried over potassium carbonate, and distilled. After redistillation 2 : 2 : 6-tetramethyltetrahydrothiopyran (I) (2 g.) was obtained as a colourless liquid, b. p. 66°/12 mm., n_D^{18} 1.4763 (Found : C, 68.3; H, 11.6; S, 20.1. $\text{C}_{10}\text{H}_{20}\text{S}$ requires C, 68.4; H, 11.4; S, 20.2%). On standing for 1–3 days at 0° with twice its

own volume of methyl iodide, the product yielded white crystals of a *methiodide*, which recrystallised from ethanol-petrol (b. p. 60–80°) on cooling below –20°; m. p. 130° (decomposition occurred from 130° to 160°) (Found: I, 40.8. $C_{11}H_{23}IS$ requires I, 40.5%). Reaction with excess of methyl iodide for 16 hours at 100° gave crystals, which after being washed with a little methanol and recrystallised from ethanol (absolute) yielded needles of trimethylsulphonium iodide, decomp. ca. 200° (Found: I, 61.8; S, 15.5. Calc. for C_3H_7IS : I, 62.2; S, 15.7%).

Synthesis of 2:2:6-Trimethyl-6-ethyltetrahydrothiopyran (V).—Glutaric anhydride. Glutaric acid (290 g.) and acetic anhydride (400 ml.) were heated under reflux for 2 hours; the acetic acid was then distilled off, and the heating continued with a further 300 ml. of acetic anhydride. After removal of the acetic acid and anhydride, glutaric anhydride (235 g., 96%) was distilled over at 150°/10 mm. [Despite the claims of Krafft and Noerdlinger (*Ber.*, 1889, 22, 817) that glutaric acid is wholly dehydrated by refluxing alone for 2–3 hours, it was not found possible to complete the conversion into the anhydride by this method.]

Methyl hydrogen glutarate (see Clutterbuck and Raper, *loc. cit.*). Glutaric anhydride (235 g.) and methanol (132 g., 2 mols.) were refluxed for 1 hour, and the product, after removal of methanol, was distilled at 10 mm. The distillate consisted of methyl glutarate, methyl hydrogen glutarate, and some glutaric acid. The first and the last fraction were combined with glutaric acid extracted from the residue, and were reconverted into glutaric anhydride (*via* the acid) and re-esterified with methanol. The overall yield of methyl hydrogen glutarate was 240 g. (80%), b. p. 147–151°/10 mm., n_D^{20} 1.4372.

Glutaric acid half ester half chloride. A mixture of the acid ester (240 g.) and thionyl chloride (720 g.) was warmed until gas evolution started, and then very gently for one hour and refluxed for a further hour. After removal of excess thionyl chloride, the product (258 g., 97%) distilled at 98°/10 mm.

Methyl δ -Ketoheptate (II).—An ethereal solution of ethylmagnesium bromide was prepared from magnesium (42 g.) and ethyl bromide (188 g.). Powdered cadmium chloride (288 g.), rendered completely anhydrous by being heated for 1 hour on a sand-bath and allowed to cool in a desiccator over phosphoric oxide, was slowly added with stirring to the Grignard solution cooled in ice. When the solution set nearly solid it was necessary to add more ether and shake vigorously during the addition of the remaining chloride. The ice-bath was then removed, and the mixture stirred for 30 minutes. Absence of excess of Grignard reagent was ensured by testing with Michler's ketone.

To the solution of ethylcadmium bromide (10% excess reckoned on cadmium chloride) at 0° was slowly added with vigorous stirring the half ester half chloride (258 g.) in ether (300 ml.). When the mixture set solid more ether was introduced, and the addition was continued with constant shaking. After refluxing for 1 hour on the steam-bath, the mixture was diluted with ice, and then dilute sulphuric acid was added until the precipitate just dissolved. The ether layer was separated and was shaken successively with dilute aqueous ammonia, dilute sulphuric acid, dilute aqueous sodium hydrogen carbonate, and water. After drying over magnesium sulphate and removal of ether, the product was distilled at 104–110°/10 mm. Refractionation gave 144 g. (58%) of methyl δ -ketoheptate, b. p. 108°/10 mm., n_D^{20} 1.4296. On standing for several days with semicarbazide hydrochloride and potassium acetate in aqueous alcohol, the ester yielded a *semicarbazone*, which recrystallised from 95% alcohol to give colourless plates, m. p. 113° (Found: C, 50.2; H, 7.9; N, 19.6. $C_8H_{17}O_3N_2$ requires C, 50.2; H, 7.9; N, 19.6%).

2:6-Dimethyloctane-2:6-diol (III).—An ethereal solution of methylmagnesium iodide (3.25 mol.), prepared from magnesium (40.5 g.) and methyl iodide (236 g.), was stirred at 0° during the gradual introduction of methyl δ -ketoheptate (70 g.) in ether (100 ml.). When addition was complete, the solution was refluxed for 4 hours and then allowed to stand over the week-end. The product was decomposed with a solution of ammonium chloride (105 g.) in water (1500 ml.) at 0°, and the ether layer was separated. The aqueous layer was evaporated down to ca. 1200 ml., and constantly extracted with ether for 40 hours. After drying, and removal of ether, the 2:6-dimethyloctane-2:6-diol from the combined extracts was distilled at 87–90°/0.1 mm. The diol (60 g., 78%) was a colourless viscous liquid, n_D^{20} 1.4563, which at 0° slowly crystallised to give an oily white solid, m. p. 25–37°, and slowly sublimed at 20°/10⁻⁵ mm. to white crystals, m. p. 47–49.5° (Found: C, 68.1; H, 12.2. $C_{10}H_{22}O_2$ requires C, 69.0; H, 12.6%).

2:2:6-Trimethyl-6-ethyltetrahydrothiopyran (IV).—2:6-Dimethyloctane-2:6-diol (28 g.) was vigorously stirred for 30 minutes at 100° with 2*N*-sulphuric acid (250 ml.). The residual oil was combined with an ether extract of the aqueous layer, and dried over potassium carbonate. After removal of ether the product (12 g., 48%) distilled over at 65–74°/0.1 mm.; dimethyloctadiene was obtained in the lower-boiling fractions (ca. 34°/1 mm.). Refractionation of the product gave 2:2:6-trimethyl-6-ethyltetrahydrothiopyran, a mobile, colourless, sweet-smelling liquid, b. p. 89°/10 mm., n_D^{20} 1.4508 (Found: C, 76.7; H, 12.8. $C_{10}H_{20}O$ requires C, 76.9; H, 12.8%).

2:2:6-Trimethyl-6-ethyltetrahydrothiopyran (V).—An intimate mixture of 2:2:6-trimethyltetrahydrothiopyran (12 g.) and phosphorus pentasulphide (35 g.) was heated for 5 hours at 100° in a Carius tube sealed under nitrogen. The solid oily residue was extracted thoroughly with ether, then decomposed by water, and the aqueous solution extracted with ether. The ethereal extract was shaken 3 times with 10% aqueous sodium hydroxide and subsequently dried over magnesium sulphate. After removal of ether, the product (3.5 g., 26%) distilled over at 40°/0.2 mm. After 2 further fractional distillations 2:2:6-trimethyl-6-ethyltetrahydrothiopyran was obtained as a mobile, colourless liquid with a characteristic odour, b. p. 87°/13 mm., n_D^{20} 1.4849 (Found: C, 69.6; H, 11.7; S, 18.6. $C_{10}H_{20}S$ requires C, 69.8; H, 11.6; S, 18.6%). When this was kept with methyl iodide at 0°, the methiodide slowly separated as a red oil, but reaction at 100° (20 hours' reaction in a tube sealed under nitrogen) gave trimethylsulphonium iodide (Found: C, 15.7; I, 61.9. Calc. for C_3H_7IS : C, 15.7; I, 62.2%).

This paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The author wishes to express his thanks to Dr. E. H. Farmer for his helpful advice and criticism.

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[Received, November 26th, 1946.]

NOTES.

Activating Influence of para-Groups on the Lability of Chlorine in Chlorobenzenes.

By G. M. BADGER, J. W. COOK, and (Miss) WENDY P. VIDAL.

IN another investigation, the activating influence of the azo-group on a *p*-chloro-substituent towards reaction with an anionoid reagent (compare Borsche and Exss, *Ber.*, 1923, 56, 2353) appeared to be somewhat greater than expected, and the present work was undertaken to obtain a quantitative measure of this effect. For this purpose, the percentage reaction with piperidine of various *p*-substituted chlorobenzenes has been determined, under standard conditions, by the gravimetric estimation of the halide ion in the reaction mixture, a method essentially the same as that used by Sandin and Liskear (*J. Amer. Chem. Soc.*, 1935, 57, 1304). A preliminary trial of the method of Brewin and Turner (*J.*, 1928, 332), which involves weighing the piperidine salt which separates out on cooling the reaction mixture, gave much lower results than were obtained by the method of Sandin and Liskear. This was, no doubt, due to the uncertainty as to the composition of the precipitated salt (Powell and Dehn, *J. Amer. Chem. Soc.*, 1917, 39, 1717), and also to the fact that piperidine hydrochloride is not completely insoluble in benzene.

Materials.—As solvent, sodium-dried, thiophen-free benzene, was used. Piperidine was dried over potassium hydroxide and kept over this reagent after being distilled. The *p*-chloronitrobenzene was a commercial sample, recrystallised from alcohol, m. p. 83°. *p*-Chloroaniline was also a commercial sample, recrystallised from benzene, m. p. 70°. *p*-Chloroazobenzene, prepared by the method of Jacobson and Loeb (*Ber.*, 1903, 36, 4090) and recrystallised from alcohol, had m. p. 89°. *p*-Chlorobenzonitrile was prepared from *p*-chlorobenzamide by dehydration with phosphoric oxide; recrystallised from aqueous alcohol, it had m. p. 91°. Chlorobenzene was redistilled, b. p. 130°.

Method.—The *p*-substituted chlorobenzene (0.024 mol.) was heated under reflux in an all-glass apparatus, with piperidine (0.1 mol.) in anhydrous benzene (50 c.c.) for 8 hours. The aqueous extract, after being washed with a little benzene, was acidified with dilute nitric acid (5 c.c.) and the halide precipitated as silver chloride with 0.1N-silver nitrate. The precipitate was collected in a Gooch crucible and dried at 100°.

Results.—The following percentage reactions were obtained: *p*-chloronitrobenzene, 12.9, 12.9%; *p*-chlorobenzonitrile, 5.0%; *p*-chloroazobenzene, 1.97, 1.96%; chlorobenzene, 1.29, 1.31%; *p*-chloroaniline, 1.23, 1.24%.

The activating influence of the azo-group is, under these conditions, less than that of the cyano-group, and considerably less than that of the nitro-group. The amino-group exerts little effect.

One of us (G. M. B.) has been working with an Imperial Chemical Industries Research Fellowship.—UNIVERSITY OF GLASGOW. [Received, October, 24th, 1946.]

An Improved Preparation of 1:8-Dinitronaphthalene. By HERBERT H. HODGSON and EDWARD R. WARD.

WHEREAS 1:8-dinitronaphthalene is scarcely attacked by aqueous sulphide even at 90° (Hodgson and Walker, *J.*, 1933, 1346; E.P. 392,914), it is rapidly converted in methanol suspension by a mixture of sodium sulphide and sodium hydrogen carbonate into sulphide dyes (Hodgson and Ward, *J.*, 1945, 794). When, however, the mixture of 1:5- and 1:8-dinitronaphthalene obtained by nitration of α -nitronaphthalene (Hodgson and Walker, *J.*, 1933, 721) is treated by the above sodium sulphide-sodium hydrogen carbonate mixture in methanol, in amount just sufficient to reduce the whole of the 1:5-dinitronaphthalene (about one-third, as determined by the complete removal of the 1:8-isomeride with sodium sulphite), the 1:8-dinitronaphthalene is entirely unattacked and remains behind after extraction with hydrochloric acid of the 5-nitro-1-naphthylamine mixed with it. Only one crystallisation of the residue from toluene is necessary for obtaining practically pure 1:8-dinitronaphthalene in almost quantitative amount.

The finely divided mixture (10 g.) of 1:5- and 1:8-dinitronaphthalene was suspended in boiling methanol (150 c.c.) and treated with the reducing agent (14 c.c.) [prepared by dissolution of crystalline sodium sulphide (24 g.) and sodium hydrogen carbonate (8 g.) in water (40 c.c.)] added in one batch, and the boiling was continued for 5 minutes; ice chips were then added quickly to the reddish-brown mixture before pouring it into water (total volume ca. 1 l.). No sulphide was present at the end of the reaction. The solid was filtered off, washed with water, and then extracted 4 times with boiling 8% hydrochloric acid (400 c.c. per time); the yield of extracted 5-nitro-1-naphthylamine was 8% of the original mixture and ca. 24% of the 1:5-dinitronaphthalene originally present. The acid-extracted residue, after being washed with water, was dried, and extracted twice with boiling toluene (200 c.c.); on concentration, the filtered toluene extract afforded 1:8-dinitronaphthalene (6.3 g., i.e., 63% of the original mixture and ca. 95–96% of the amount of 1:8-dinitronaphthalene present; cf. the crude yield of ca. 40% obtained by Hodgson and Walker, *loc. cit.*), m. p. 169–171.5°. Increasing the amount of reducing agent beyond that used above lowered the yield of 1:8-dinitronaphthalene and also the purity of the 5-nitro-1-naphthylamine.

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals, and the Department of Scientific and Industrial Research for a Senior Research Award (to E. R. W.). TECHNICAL COLLEGE, HUDDERSFIELD. [Received, October 25th, 1946.]

OBITUARY NOTICE.

BEVAN LEAN.

1865—1947

BEVAN LEAN received his early education at Ackworth School, near Pontefract, and at Bootham School, York. He proceeded in 1887 to Owens College, Manchester, to study chemistry, where his exceptional ability was soon recognised. He held the Dalton Scholarship for research in 1891 and the Berkeley Fellowship in 1893, and was appointed to the staff of the Chemistry Department as Assistant Lecturer and Demonstrator in 1894. As a student he was resident at Dalton Hall, and was Tutor in Chemistry there from 1889 to 1894.

During these years at Manchester Lean was actively engaged in research, and was author or part author of six papers in the *Transactions* of the Chemical Society, published in the years 1892—1900. The first of these, with W. A. Bone, was on the "Behaviour of Ethylene on Explosion with less than its own Volume of Oxygen", but the remainder showed that his chief interest lay in the realm of synthetical organic chemistry and dealt with butanetetracarboxylic acids, their homologues, and derived compounds. He took the external London Degrees of B.Sc. (1889) and D.Sc. (1894).

In 1897 Lean forsook an assured academic future to devote his life to school teaching. After four years as science master at Ackworth, he was appointed Headmaster of the Friends' school at Sidcot, Somerset, a position which he held for twenty-eight years. While there, he published with W. H. Perkin, Junr., in 1909 "An Introduction to Chemistry and Physics". Lean was himself a lifelong member of the Society of Friends, and was deeply religious. Under his influence the school developed greatly, and the discipline of his scientific training and his whole-hearted devotion to the welfare of the school and the individual scholars combined to make him a headmaster of outstanding ability who won the respect and affection of many generations of Sidcot scholars. He leaves a widow and two sons. The elder, Oscar B. Lean, is in medical practice, and the younger, Owen B. Lean, is an entomologist with Imperial Chemical Industries Ltd.

W. BAKER.

209. *Amidines. Part VII. Preparation of Amidines from Cyanides, Aluminium Chloride, and Ammonia or Amines.*

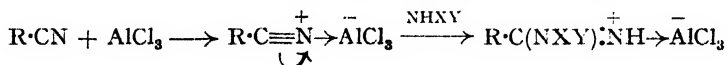
By P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT.

Amidines and *N*-substituted amidines can be prepared from cyanides, aluminium chloride, and ammonia or an amine. The method gives good yields of *NN*-dialkylamidines, which are obtained in poor yield by the ammonium sulphate method.

THE preparation of amidines from cyanides and ammonium or substituted ammonium sulphates was described in Part I (Oxley and Short, *J.*, 1946, 147), in which the production of *NN*-disubstituted amidines was illustrated by a single example, namely *NN*-diphenylbenzamidine, obtained in 29% yield from phenyl cyanide and diphenylammonium benzenesulphonate. Application of the method to *p*-cyanophenyl methyl sulphate and piperidinium benzenesulphonate afforded *NN*-*pentamethylene-p*-methylsulphonylbenzamidine (27%), but our initial attempts to bring about a similar reaction with diethylammonium benzenesulphonate were unsuccessful. On raising the reaction temperature to 280°, however, *N*-ethyl-*p*-methylsulphonylbenzamidine was obtained in 0.8% yield, rising progressively to 4.5% at 325°. The same amidine was obtained from the cyanide and triethylammonium benzenesulphonate at 305° (0.2%), ethylammonium benzenesulphonate at 280° (41%), or ethylammonium chloride at 250°. (We find that it is essential to use the ammonium salt of a sulphonic acid or ammonium thiocyanate in order to obtain reasonable yields of unsubstituted amidines, but mono- and dialkylammonium chlorides may give good yields of substituted amidines.) Ammonium benzenesulphonate (81%) was obtained when diethylammonium benzenesulphonate and phenyl cyanide were heated at 350° and little cyanide was recovered. Similarly, piperidinium benzenesulphonate and phenyl or benzyl cyanide at 300° gave ammonium benzenesulphonate and benzamidinium or phenylacetamidinium benzenesulphonate. These dealkylations recall the progressive dealkylation of trialkylammonium chlorides on heating (Hofmann, *Proc. Roy. Soc.*,

1860, 10, 595; Fileti and Piccini, *Ber.*, 1879, 12, 1508) and Werner's observation (*J.*, 1914, 105, 2769) that whereas ammonium methyl sulphate rearranges to methylammonium hydrogen sulphate and undergoes some demethylation above 240°, ammonium ethyl sulphate is completely decomposed on heating into ammonium hydrogen sulphate and ethylene. We ultimately found that a 7% yield of *NN*-diethyl-*p*-methylsulphonylbenzamidinium could be obtained from the cyanide and diethylammonium benzenesulphonate at 224° and was identical with a specimen prepared by the Pinner method. *NN*-Diethylbenzamidinium was prepared by the Pinner method and its *toluene-p*-sulphonate was almost completely decomposed at 215–250° into phenyl cyanide and diethylammonium *toluene-p*-sulphonate. These observations indicate that the sulphonate method is unlikely to be generally suitable for the preparation of *NN*-dialkylamidines.

The few cyanides which are known to combine directly with ammonia or amines to yield amidines contain polar groups which stimulate the additive capacity of the cyano-group (Part I, *loc. cit.*), and it seemed probable that the reactivity of cyanides could be stimulated, as is the case with carbonyl compounds, by combination with a catalyst having strong kationoid properties. A number of alkyl cyanide-aluminium chloride complexes have been described (Genvresse, *Bull. Soc. chim.*, 1888, 49, 341; Perrier, *Compt. rend.*, 1895, 120, 1424; *Bull. Soc. chim.*, 1895, 13, 1031), and it seemed likely that catalysts of the Friedel-Crafts type might enhance the dipole condition of the molecule and with it its reactivity:



On the other hand, aluminium chloride and similar kationoid compounds readily yield amines with ammonia and amines, so that the efficiency of the catalyst would be reduced by the presence of the competitive anionoid centre in the base and would also depend upon the solubility of the respective complexes in the reaction mixture. Thus, *p*-cyanophenyl methyl sulphone and aluminium chloride yielded an insoluble brown complex which gave only traces of amidine (Fuller reaction; *Nature*, 1944, 154, 773) when heated with ammonia in various solvents, but *p*-methylsulphonylbenzamidinium was obtained in 54% yield when the cyanide and aluminium chloride were heated with excess of molten urea, which acts as a source of ammonia and as a solvent. A number of amidines have been prepared by heating a cyanide and aluminium chloride with a base, and the scope of the method is illustrated by the examples in the Table. It will be noted that the method affords good yields of *NN*-dialkylamidines and is therefore a useful supplement to the ammonium sulphonate method.

Amidine (a).	Yield, %.	Amidine (a).	Yield, %.
Benzamidinium (b)	57	<i>N</i> -2-Pyridyl- <i>p</i> -methylsulphonylbenz-	
<i>o</i> -Nitrobenzamidinium (c)	13	amidinium	73.5
<i>p</i> -Nitrobenzamidinium (c)	60	<i>N</i> -cyclohexylphenylacetamidinium	90
<i>p</i> -Methylsulphonylbenzamidinium (c)	54	<i>N</i> -cyclohexyl-1-amidino- <i>n</i> -heptane	98
β -Naphthamidinium (c)	3.8	1 : 3-Bis-(<i>N</i> -phenyl-4-amidinophenoxy)-	
<i>N</i> -Phenylacetamidinium (d)	50.5	propane	69
<i>N</i> -cyclohexyldiethylacetamidinium	28	<i>NN</i> -Pentamethylenebenzamidinium	37
<i>N</i> -Benzylbenzamidinium	63	<i>N</i> -Phenyl- <i>N</i> -methylbenzamidinium	ca. 100
<i>N</i> - <i>o</i> -Nitrophenylbenzamidinium	15	<i>NN</i> -Diethyl- <i>p</i> -methylsulphonylbenz-	
<i>N</i> -2-Pyridylbenzamidinium	62	amidinium	ca. 100
<i>N</i> -Benzylanisamidinium	82.5	<i>NN</i> -Pentamethylene- <i>p</i> -methylsulphonyl-	
<i>N</i> -cyclohexylanisamidinium	94	benzamidinium	98
<i>N</i> -Phenyl-2 : 4-dichlorobenzamidinium ...	74	<i>NN</i> -Diphenylpicolinamidinium	76

(a) The product was isolated as base, hydrochloride, picrate, or benzenesulphonate (see experimental section): the yields recorded refer to the pure compound first isolated and are based on the cyanide employed.

(b) Gaseous ammonia used.

(c) Urea (16 mols.) employed as source of ammonia.

(d) *NN*-Diphenylacetamidinium (3.9%) was also formed.

We have made a cursory examination of the use of other catalysts for the production of amidines since it might be desirable to avoid the use of aluminium chloride in certain cases. Several catalysts used in reactions of the Friedel-Crafts type, such as ferric chloride, zinc, chloride, and stannic chloride, have been found to promote the formation of amidines, and other compounds exhibiting kationoid activity were also effective (see Table below). Boron trifluoride failed to promote the union of benzyl cyanide and cyclohexylamine at 140°; this may be due to the stability of monoaminoboron trifluoride.

Catalyst.	Amidine.	Yield, %.
Ferric chloride	<i>p</i> -Nitrobenzamidinium (a)	30
Zinc chloride	Phenylacetamidinium (a)	33
	<i>p</i> -Nitrobenzamidinium (a)	38
	<i>N</i> -Phenylbenzamidinium	31
	<i>N</i> -cyclohexylphenylacetamidinium	6
Stannic chloride	<i>p</i> -Nitrobenzamidinium (a)	56
Triphenyltin chloride	<i>p</i> -Methylsulphonylbenzamidinium	74
Triphenylaluminium	<i>NN</i> -Pentamethylene- <i>p</i> -methylsulphonylbenzamidinium	32
Aluminium isopropoxide	<i>p</i> -Methylsulphonylbenzamidinium	Trace
Triphenyl borate	Benzamidinium	60
	<i>NN</i> -Pentamethylene- <i>p</i> -methylsulphonylbenzamidinium	3.5
	<i>p</i> -Methylsulphonylbenzamidinium (b)	60

(a) Urea used as source of ammonia.

(b) Tribenzyl borate was ineffective.

EXPERIMENTAL.

Cyanides and Substituted Ammonium Benzenesulphonates.

Benzamidinium.—Phenyl cyanide (10 g.) and piperidinium benzenesulphonate (25 g.; 1.06 mols.) were heated at 300° for 14 hours and afforded benzamidinium benzenesulphonate, m. p. and mixed m. p. 175—175.5° (5 g., 18.5%), and ammonium benzenesulphonate, m. p. and mixed m. p. 283—285° (6.2 g., 36.5%).

Phenylacetamidinium.—Benzyl cyanide (10 g.) and piperidinium benzenesulphonate (12.5 g.; 1 mol.) similarly gave phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 186—186.5° (2.4 g., 16%), and ammonium benzenesulphonate, m. p. and mixed m. p. 283—285° (2.7 g., 30%), after 14 hours at 300°.

***N*-Ethyl-*p*-methylsulphonylbenzamidinium.**—(a) A mixture of *p*-methylsulphonylphenyl cyanide (9.05 g.) and ethylammonium benzenesulphonate (10.15 g.; 1 mol.) was heated at 275—280° for 80 minutes and the residue was recrystallised from hot water (100 c.c.), giving recovered cyanide (2 g.), m. p. and mixed m. p. 140—141°. The aqueous solution was extracted with chloroform and made alkaline with 5*N*-sodium hydroxide, and the amidine (4.6 g.; 41%) was collected in chloroform. This amidine was obtained as a gum, but *N*-ethyl-*p*-methylsulphonylbenzamidinium picrate had m. p. 155.5—156° (Found: N, 15.4. C₁₈H₁₇O₆N₃S requires N, 15.4%). The toluene-*p*-sulphonate had m. p. 242° (Found: C, 51.2; H, 5.6; N, 7.2; S, 15.9. C₁₇H₁₈O₃N₂S₂ requires C, 51.25; H, 5.5; N, 7.0; S, 16.1%).

(b) A mixture of the cyanide (5 g.) and ethylammonium chloride (5 g.; 2.2 mols.) was heated at 250° for an hour and afforded 1.3 g. of recovered cyanide and 3.5 g. (56%) of crude amidine which gave 3.7 g. (34%) of pure toluene-*p*-sulphonate, m. p. and mixed m. p. 242°. After 3½ hours at 224° a mixture of the cyanide (5.43 g.) and ethylammonium chloride (9.8 g.; 4 mols.) afforded 27.6% of recovered cyanide and 43% of amidine, isolated as toluene-*p*-sulphonate. The following experiments with 5.43 g. of cyanide and 2.45 g. (1 mol.) of ethylammonium chloride illustrate the influence of experimental conditions on the yield of amidine.

Temp.	200—202°	224°	224°	224°	230°
Time, hrs.	1	2	4	14	1
Recovered cyanide, %	92	51.6	44.2	38.7	64.5
Yield of amidine, %*	2.85	15.9	26.7	32.3	17.9

* Isolated as toluene-*p*-sulphonate, m. p. 242°.

(c) *N*-Ethyl-*p*-methylsulphonylbenzamidinium was also produced when the cyanide (5.5 g.) and diethylammonium benzenesulphonate (7 g.; 1 mol.) were heated at temperatures within the range 280—326°. The reaction mixture was worked up as described in (a), and the principal basic product was identified by the analysis and mixed m. p. of its toluene-*p*-sulphonate. Before purification this salt gave a faint Fuller reaction and therefore probably contained traces of *p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate. The mother liquors may have contained *NN*-diethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate as a minor constituent. The results are summarised in the following table.

Temp.	280°	295°	310—312°	325—326°
Time, hrs.	2	½	½	½
Recovered cyanide, %	85	82	71	42
<i>N</i> -Ethyl- <i>p</i> -methylsulphonylbenzamidinium toluene- <i>p</i> -sulphonate (m. p. 242°), %	0.83	1.65	3.6	4.55

(d) Triethylammonium benzenesulphonate, prepared from its constituents and crystallised from isopropanol to constant m. p., formed hexagonal plates, m. p. 119° (Found: N, 5.5. Calc. for C₁₂H₂₁O₃NS: N, 5.4%). Norton and Westenhoff (*Amer. Chem. J.*, 1888, 10, 133) record m. p. 120—121°. A mixture of this salt (12.95 g.; 1 mol.) and *p*-methylsulphonylphenyl cyanide (9.05 g.) was heated at 305—306° for 30 minutes. Gas evolution began at ca. 240° and continued throughout, the odour first resembling that of ethylamine but subsequently changing to that of a heterocyclic base. The product, which solidified on cooling, afforded 6.3 g. (70%) of recovered cyanide, m. p. 141—142°, and 0.55 g. of a crude base, from which only 0.04 g. (0.2%) of *N*-ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate, m. p. and mixed m. p. 242°, was obtained.

***N*-Methyl-*p*-nitrobenzamidinium.**—A mixture of *p*-nitrophenyl cyanide (7.4 g.) and methylammonium chloride (3.9 g.; 1.2 mols.) became homogeneous after an hour's heating at 224° and after a further

3 hours at this temperature afforded 4.3 g. of recovered cyanide, m. p. 147°, and 0.7 g. (8%) of *N*-methyl-*p*-nitrobenzamidinium, m. p. 137.5° (Found: N, 23.4. $C_8H_8O_2N_3$ requires N, 23.5%). The picrate crystallised from isopropanol in needles, m. p. 174.5° (Found: N, 20.6. $C_{14}H_{11}O_9N_4$ requires N, 20.6%).

NN-Diethylbenzamidinium.—Benziminoethyl ether (10 g.; b. p. 106–108°/16 mm., Wheeler, Walden, and Metcalf, *Amer. Chem. J.*, 1898, 20, 71), diethylammonium benzenesulphonate (15.5 g.; 1 mol.), and anhydrous ethanol (20 c.c.) were kept at 50° for 21 hours, then cooled and filtered to recover diethylammonium benzenesulphonate (6.5 g.). The filtrate was evaporated under diminished pressure and the residue was shaken with 2*N*-sodium hydroxide and chloroform. The dried chloroform solution was evaporated and the residue distilled. The first fraction, b. p. 65–85°/3 mm. (1 g.), smelled of phenyl cyanide, and the amidine, b. p. 85–90° (almost entirely at 88–89°/3 mm.) (6.1 g., 51.6%), then distilled leaving a residue (1.5 g.) of 2 : 4 : 6-triphenyl-1 : 3 : 5-triazine, m. p. 236° (Found: C, 81.5; H, 5.1; N, 13.6. Calc. for $C_{21}H_{15}N_3$: C, 81.55; H, 4.9; N, 13.6%). Robin (*Ann. Chim.*, 1921, 16, 113) records m. p. 235°. *NN*-Diethylbenzamidinium picrate crystallised from methanol in plates, m. p. 161° (Found: N, 17.35. $C_{17}H_{19}O_7N_5$ requires N, 17.3%), and the toluene-*p*-sulphonate had m. p. 126° (Found: N, 8.1. $C_{18}H_{21}O_3N_3S$ requires N, 8.05%). When the imino-ether, benzenesulphonate, and ethanol were refluxed for 14 hours (internal temperature 90°), the yield of amidine was 5.1 g. (43%).

NN-Diethylbenzamidinium toluene-*p*-sulphonate began to decompose with evolution of phenyl cyanide at 215–220°, and after $\frac{1}{2}$ hour at 250° the residue afforded diethylammonium toluene-*p*-sulphonate, m. p. and mixed m. p. 103°, after being washed with ether and crystallised from isopropanol-ether (Found: N, 5.7. Calc. for $C_{11}H_{13}O_3NS$: N, 5.7%). Norton and Otten (*Amer. Chem. J.*, 1888, 10, 140) record m. p. 88°.

Considerable pressure was developed when phenyl cyanide (8.5 g.) and diethylammonium benzenesulphonate (19 g.; 1 mol.) were heated in a sealed tube for 22 hours at 345–350°. The resulting mixture of brown oil and colourless plates was triturated with chloroform and gave ammonium benzenesulphonate, m. p. and mixed m. p. 283–285° (11.6 g., 81%). The oil isolated from the chloroform solution distilled over a very wide range and afforded neither fractions of constant boiling point nor crystalline picrates.

NN-Diethyl-*p*-methylsulphonylbenzamidinium.—(a) A solution of *p*-methylsulphonylphenyl cyanide (9.05 g.) in ethanol (2.5 g.; 1.1 mols.) and chloroform (60 c.c.) was treated with a current of hydrogen chloride until 2.3 g. (1.3 mols.) had been absorbed. The imino-ether hydrochloride (8.4 g.), m. p. 220–225° (decomp.), was collected after being kept for 60 hours at room temperature (cf. Fuller, Tonkin, and Walker, *J.*, 1945, 636; Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, B, 133, 46). The imino-ether (5.6 g., 49%), obtained as a viscous gum by shaking the hydrochloride with 5*N*-sodium hydroxide and chloroform, was heated with diethylammonium benzenesulphonate (6 g.; 1.05 mols.) for $\frac{1}{2}$ hours at 140°. Alcohol was evolved, and trituration of the crystalline product with chloroform afforded an almost insoluble solid (0.35 g.) which separated from pyridine in colourless needles, m. p. >360°, and was probably 2 : 4 : 6-tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine (Found: N, 8.0. $C_{24}H_{21}O_6N_3S_3$ requires N, 7.7%). Concentration of the chloroform solution afforded recovered cyanide (1.3 g., m. p. and mixed m. p. 141°) and then the crude amidine (2 g., 32%) which gave a picrate, m. p. 184.5°, identical with that obtained from *NN*-diethyl-*p*-methylsulphonylbenzamidinium prepared by the aluminium chloride method (below).

(b) The cyanide (4.5 g.) and diethylammonium benzenesulphonate (23.1 g.; 4 mols.), heated at 224° for 14½ hours, afforded 3.5 g. of recovered cyanide and the crude amidine (0.5 g., 8%) which afforded the pure picrate, m. p. and mixed m. p. 184.5° (0.83 g., 7%). Almost the same yields were obtained when diethylammonium chloride (11 g.; 4 mols.) was used in place of the benzenesulphonate and the mixture heated at 224° for 2½ hours.

(c) The preparation of this amidine by the aluminium chloride method is described below.

NN-Pentamethylene-*p*-methylsulphonylbenzamidinium.—*p*-Methylsulphonylphenyl cyanide (4.5 g.) and piperidinium benzenesulphonate (24.3 g.; 4 mols.) were heated at 230° for 4 hours and gave 2.4 g. of recovered cyanide and 1.8 g. (27%) of *NN*-pentamethylene-*p*-methylsulphonylbenzamidinium, m. p. 97°. The amidine afforded a toluene-*p*-sulphonate, m. p. 230–231°, and there was no depression in m. p. on admixture of the amidine and its salt with preparations made by the aluminium chloride method (see below).

Preparation of Amidines from Cyanides, Bases, and Kationoid Reagents.*

Except where otherwise indicated, the cyanide and the base were employed in the proportion of one mol. of base per cyano-group, and one mol. of aluminium chloride (reckoned as $AlCl_3$) or of zinc chloride was added to the mixture. The experimental conditions used varied considerably and did not appear to be critical. The yields recorded are not necessarily the highest obtainable since a systematic examination of the effect of conditions on the yield of amidine was made in only a few cases. The reaction product, consisting of a complex of the amidine with the catalyst, was carefully decomposed with water and, when the amidine hydrochloride was sparingly soluble in water, it separated on cooling from the hot, filtered solution. Usually, however, the amidine was liberated from the solution by excess of aqueous sodium hydroxide, collected in chloroform, and then isolated as base, picrate, or hydrochloride. The methods employed follow closely those described in previous parts of this series, to which reference is made for earlier descriptions of many of the amidines (Part I, Oxley and Short, *J.*, 1946, 147; Part II, Oxley, Robson, Partridge, and Short, *ibid.*, p. 763; Part III, Oxley and Short, this vol., p. 382; Part IV, Partridge and Short, *ibid.*, p. 390; Part V, Hullin, Miller, and Short, *ibid.*, p. 394).

Benzamidinium.—(a) A mixture of phenyl cyanide (2.1 g.) and aluminium chloride (5.3 g.; 2 mols.) was heated at 100° for 30 minutes in an atmosphere of dry ammonia, and the amidine was isolated as picrate, m. p. and mixed m. p. 239–240°. Yield, 3.95 g.

(b) Phenyl cyanide (2.06 g.), ammonium benzenesulphonate (3.5 g.; 1 mol.), and triphenyl borate

* See also B.P. Applns. 22748 and 22749 (4.9.1945).

(5.8 g.; 1 mol.) gave a 60% yield of benzamidinium benzenesulphonate, m. p. and mixed m. p. 175—175.5°, when heated at 160° in a stream of dry ammonia for 5 hours.

o-Nitrobenzamidinium.—*o*-Nitrophenyl cyanide (5.6 g.), aluminium chloride (5 g.), and urea (36 g.; 16 mols.) were heated at 180° for 2 hours with vigorous stirring. The amidine was isolated as picrate, m. p. 228—229° (Found : N, 21.4. Calc. for $C_{13}H_{10}O_6N_6$: N, 21.3%). Yield, 1.9 g. The m. p. of *o*-nitrobenzamidinium picrate is recorded in Part I as 232—233° (decomp.).

p-Nitrobenzamidinium.—(a) This amidine was prepared from *p*-nitrophenyl cyanide (1.5 g.), aluminium chloride, and urea in the proportions used in the previous example, and was isolated either as base, m. p. 216° (decomp.), or as picrate, m. p. 239—240° (Part I). After 15 minutes at 180° the yield was 26% and rose to 60% after 30 minutes. When only 8 mols. of urea were employed, the reaction mixtures solidified after 20 minutes and the yield of *p*-nitrobenzamidinium was only 4%.

(b) A mixture of *p*-nitrophenyl cyanide (1.5 g.), urea (9.6 g.; 16 mols.), and zinc chloride (1.4 g.) afforded a homogeneous mixture after being stirred at 180° for 15 minutes, and after another 15 minutes at this temperature the yield of amidine, m. p. 212°, was 38%.

(c) A 9.1% yield of amidine was obtained when the cyanide (3 g.) and zinc chloride (2.8 g.) were heated at 180° for 15 minutes in a stream of ammonia. After 15 minutes at 135—140° the yield was 1.5%.

(d) When *p*-nitrophenyl cyanide (1.5 g.), urea (9.6 g.; 16 mols.), and anhydrous ferric chloride (1.6 g.) were heated to 120°, an exothermic reaction raised the temperature to 180°, and the cooled reaction mixture then afforded a 30% yield of the amidine.

(e) The cyanide (1.5 g.), urea (2.4 g.; 4 mols.), and stannic chloride (2.6 g.) afforded a 56% yield of amidine, isolated as picrate, m. p. 230—232°, after 30 minutes at 180°. Recrystallisation from methanol raised the m. p. of the picrate to 238—239°.

p-Methylsulphonylbenzamidinium.—(a) A mixture of *p*-methylsulphonylphenyl cyanide (9 g.), aluminium chloride (6.7 g.), and urea (48 g.; 16 mols.) was heated at 180° for 30 minutes. The amidine was isolated as the picrate, m. p. and mixed m. p. 263—264° (Part IV). Yield, 11.5 g.

p-Methylsulphonylphenyl cyanide (4.5 g.) and aluminium chloride (3.3 g.; 1 mol.) afforded a brown complex when heated in benzene (250 c.c.). This solid, which softened at 95—105° and decomposed at 120—125° with gas evolution, gave a trace of amidine (Füller reaction) when heated in a stream of ammonia in various solvents. A similar result was obtained when zinc chloride, ferric chloride, or stannic chloride was substituted for aluminium chloride. Only traces of amidine were formed when the cyanide and aluminium isopropoxide were heated in ammonia at 100° or 110°, 99% of the cyanide being recovered.

(b) A mixture of *p*-methylsulphonylphenyl cyanide (1.81 g.) and triphenyltin chloride (3.85 g.; 1 mol.; Kozeschkov, Nadj, and Alexandrov, *Ber.*, 1934, 67, 1348) was heated for 24 hours at 100° in a stream of ammonia, and the amidine was isolated as *p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate, m. p. 292—293° (Found : N, 7.6. $C_{15}H_{18}O_6N_2S_2$ requires N, 7.6%). The yield was 2.75 g. (74%).

(c) A 40% yield of the toluene-*p*-sulphonate was similarly prepared from the product obtained by heating the cyanide (3.62 g.) and triphenyl borate (5.8 g.; 1 mol.) in a stream of ammonia for 17 hours at 100°. No amidine was obtained when tribenzyl borate (1 mol.) was used in place of triphenyl borate.

β-Naphthamidinium.—A mixture of *β*-naphthyl cyanide (1.5 g.), urea (9.6 g.; 16 mols.), and aluminium chloride (1.3 g.) evolved ammonia when heated but was not completely homogeneous after 1 hour at 180°. The product afforded *β*-naphthamidinium picrate (0.15 g.), m. p. 248°, and recrystallisation from methanol gave the pure product, m. p. and mixed m. p. 252° (Part I).

Phenylacetamidinium.—Phenylacetamidinium picrate (1.18 g.), m. p. and mixed m. p. 227—228° (decomp.), was prepared from the homogeneous melt obtained by heating benzyl cyanide (1.2 g.), urea (9.6 g.; 16 mols.), and zinc chloride (1.4 g.) at 180° for an hour. The same m. p. is recorded in Part IV.

N-Phenyl- and *NN'*-Diphenyl-acetamidinium.—Powdered aluminium chloride (66.6 g.) was added in portions during $\frac{3}{4}$ hour to methyl cyanide (20.5 g.) and aniline (46.5 g.) so that the temperature remained at 90—100°, and the mixture was kept at 100° for an hour. The mixture of bases (58.7 g.), isolated from the product in the usual way, afforded crystals (3.9%) of *NN'*-diphenylacetamidinium, m. p. 131—132°, on recrystallisation from aqueous methanol. A second recrystallisation from aqueous methanol afforded the pure amidine, m. p. 133.5—134° (cf. Part III). The original mother liquor was made acid to brilliant-yellow with ethanolic picric acid and the crude picrate was recrystallised from methanol giving *N*-phenylacetamidinium picrate, m. p. 194—195° (Found : N, 19.3. Calc. for $C_{14}H_{13}O_7N_5$: N, 19.3%), higher than the values previously recorded (Part III). Yield, 91.6 g.

N-cyclohexyl-*aa*-diethylacetamidinium.*—When powdered aluminium chloride (10.6 g.) was added in one portion to 1-ethylbutyl cyanide (7.7 g.; Ziegler and Ohlinger, *Annalen*, 1932, 495, 110) and cyclohexylamine (9.6 g.; 1.2 mols.), the temperature rose to about 200°. When the temperature had fallen to 100°, the product was mixed with ice (100 g.) and the solid was collected and washed with a little ether. Recrystallisation of the solid (12 g.) from 0.5*N*-hydrochloric acid (125 c.c.) afforded 5.1 g. of *N*-cyclohexyl-*aa*-diethylacetamidinium chloride, m. p. 240—242° (Found : N, 12.3. $C_{12}H_{25}N_4Cl$ requires N, 12.0%).

N-Benzylbenzamidinium.—Aluminium chloride (13.3 g.) was added with stirring during 30 minutes to phenyl cyanide (10.3 g.) and benzylamine (10.7 g.) so that the temperature remained below 120°. After 20 minutes' heating at 180°, the amidine was isolated, collected in chloroform, and converted in aqueous solution into the hydrochloride, m. p. and mixed m. p. 227—229° (Part V). The yield of hydrochloride was 10.6 g., and 8.6 g. of *N*-benzylbenzamidinium picrate, m. p. 162—164°, were obtained from the mother liquor and sodium picrate solution. Recrystallisation from ethanol raised the m. p. of the picrate to 169—170° (Part V).

N-*o*-Nitrophenylbenzamidinium.—*o*-Nitroaniline (13.8 g.) was dissolved in phenyl cyanide (10.3 g.) at 50°, finely powdered aluminium chloride (13.4 g.) was then added, and the mixture was stirred at 140°

* Preparation by Mr. J. Miller.

for 20 minutes. The amidine was liberated, collected in chloroform, dissolved in an equivalent of 5*N*-hydrochloric acid, and mixed with aqueous sodium picrate. Recrystallisation of the precipitate from aqueous cellosolve afforded *N*-*o*-nitrophenylbenzamidinium picrate, m. p. 208—209° (Found: N, 17.9. $C_{19}H_{14}O_6N_8$ requires N, 17.9%). Yield, 6.92 g.

N-2-Pyridylbenzamidine.—When aluminium chloride (6.7 g.) was added to a mixture of phenyl cyanide (5.15 g.) and 2-aminopyridine (4.7 g.) the temperature rose to 160° and the reaction was completed by heating at 200° for 15 minutes. Crystallisation of the crude amidine from light petroleum afforded *N*-2-pyridylbenzamidine, m. p. 99—99.5° (Found: N, 21.3. $C_{12}H_{11}N_3$ requires N, 21.3%). Yield, 6.1 g. The picrate crystallised from methanol in plates, m. p. 209° (Found: N, 19.9. $C_{18}H_{14}O_7N_8$ requires N, 19.7%), and the toluene-*p*-sulphonate had m. p. 171.5° (Found: N, 11.6. $C_{18}H_{15}O_3N_3S$ requires N, 11.4%).

N-Phenylbenzamidine.—A mixture of phenyl cyanide (5.2 g.), aniline (4.7 g.), and zinc chloride (6.8 g.) was heated at 110—115° for 30 minutes, and the temperature was then quickly raised to 210° to give a homogeneous melt, which was then cooled immediately. The crude amidine afforded 0.54 g. of *N*-phenylbenzamidine, m. p. and mixed m. p. 116° (Part I), on crystallisation from ethanol, and a second crop (2.5 g.), m. p. 112°, gave pure amidine (2.45 g.) when purified through the toluene-*p*-sulphonate.

N-Benzylanisamidine.—The temperature rose to about 200° when aluminium chloride (13.4 g.) was added to *p*-methoxyphenyl cyanide (13.3 g.) and benzylamine (11 g.). The product was crystallised from water giving *N*-benzylanisamidinium chloride, m. p. 225° (Found: N, 10.1. $C_{15}H_{17}ON_2Cl$ requires N, 10.1%). Yield, 22.8 g. *N*-Benzylanisamidine crystallised from light petroleum (b. p. 80—100°) in prisms, m. p. 89° (Found: N, 11.5. $C_{15}H_{16}ON_2$ requires N, 11.7%).

N-cyclohexylanisamidine.—*p*-Methoxyphenyl cyanide (6.65 g.), cyclohexylamine (6.0 g.), and aluminium chloride (7 g.), brought into reaction as described in the previous example, afforded *N*-cyclohexylanisamidinium chloride (12.6 g.), m. p. 275—276° (decomp.) (Found: N, 10.4. $C_{14}H_{21}ON_2Cl$ requires N, 10.4%). *N*-cyclohexylanisamidine, purified by sublimation in a vacuum, had m. p. 100° (Found: N, 12.3. $C_{14}H_{20}ON_2$ requires N, 12.1%), and the picrate crystallised from ethanol in needles, m. p. 141° (Found: N, 15.3. $C_{20}H_{23}O_8N_8$ requires N, 15.2%).

N-Phenyl-2:4-dichlorobenzamidine.—Powdered aluminium chloride (6.7 g.) was added during 10 minutes to a solution of 2:4-dichlorophenyl cyanide (8.6 g.) in aniline (4.7 g.) prepared at 50°. The temperature rose to ca. 130° during the addition and the reaction was completed by heating at 140° for an hour. The crude amidine (12.7 g.) was converted into *N*-phenyl-2:4-dichlorobenzamidinium chloride (11.1 g.), m. p. 147—149° (Found: N, 9.0. $C_{13}H_{11}N_2Cl_3$ requires N, 9.3%). Addition of sodium picrate to the mother liquors afforded the picrate (2.4 g.), m. p. 148—149° (Found: N, 13.9. $C_{19}H_{13}O_7N_8Cl_2$ requires N, 14.15%).

N-2-Pyridyl-*p*-methylsulphonylbenzamidine.—Aluminium chloride (4.5 g.; 0.7 mol.) was added with cooling to *p*-methylsulphonylphenyl cyanide (9.05 g.) and 2-aminopyridine (4.7 g.), and the mixture was then heated at 180° for 30 minutes. *N*-2-Pyridyl-*p*-methylsulphonylbenzamidine (10.1 g.) crystallised from methanol in colourless plates, m. p. 170.5° (Found: N, 15.5. $C_{13}H_{13}O_2N_3S$ requires N, 15.3%). The base afforded a monopicrate, m. p. 208—208.5° (Found: N, 16.4. $C_{18}H_{14}O_6N_8S$ requires N, 16.7%). Less than 0.1% of this amidine was produced when the cyanide and 2-aminopyridine benzene-sulphonate (4 mols.) were heated at 224° for 5 hours.

N-cyclohexylphenylacetamidine.—(a) The addition of aluminium chloride (13.4 g.) to benzyl cyanide (11.7 g.) and cyclohexylamine (9.9 g.) was regulated so that the temperature of the mixture did not exceed 140°, and the cold reaction product was decomposed by cold water (100 c.c.). The crude hydrochloride (22.7 g., m. p. 299—300° decomp.) was collected after cooling, and recrystallisation from water afforded *N*-cyclohexylphenylacetamidinium chloride, m. p. 301—302° (decomp.) (Found: N, 11.0. $C_{14}H_{21}N_2Cl$ requires N, 11.1%). *N*-cyclohexylphenylacetamidine crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 122.5° (Found: N, 12.95. $C_{14}H_{20}N_2$ requires N, 13.0%). The picrate had m. p. 103—105° (Found: N, 15.9. $C_{20}H_{23}O_7N_8$ requires N, 15.7%). The effect of variations in the proportion of reactants and in the reaction conditions on the yield of amidine is shown in the table below. Each experiment was performed with 11.7 g. of benzyl cyanide, and variations in the reaction time were due to the necessity of controlling the temperature in some experiments by regulating the rate of addition of aluminium chloride and in others by heating the reaction mixture.

Benzylamine (mols.).....	1	1	1	1	1	1	3	1	0.33
Aluminium chloride (mols.) ...	1	0.5	0.25	0.1	0.5	0.5	0.5	0.7	0.5
Temp.....	140°	140°	140°	140°	80°	80° *	80°	15°	80°
Time, mins.	20	20	35	35	60	150	60	60	60
Yield of amidine, %	90	88	50	33	66	31	86	7.5	78 †

* Benzene (50 c.c.) was used as solvent.

† Calculated on the amine.

(b) The temperature rose to ca. 60° when anhydrous zinc chloride (13.7 g.) was added to benzyl cyanide (11.7 g.) and cyclohexylamine (9.9 g.), and after 2 hours at 200° *N*-cyclohexylphenylacetamidine (1.2 g. or 6%), m. p. and mixed m. p. 122.5°, was isolated from the reaction product. After 30 minutes at 100° the yield of amidine was 5%.

N-cyclohexyl-1-amidino-*n*-heptane.—An exothermic reaction occurred when aluminium chloride (2.7 g.) was added to *n*-heptyl cyanide (2.5 g.) and cyclohexylamine (2 g.), and the temperature rose to ca. 200°. The reaction mixture, which was allowed to cool immediately, afforded *N*-cyclohexyl-1-amidino-*n*-heptane hydrochloride (5.1 g.), m. p. 200° (Found: N, 10.65. $C_{14}H_{29}N_2Cl$ requires N, 10.75%). The picrate had m. p. 102° (Found: N, 15.6. $C_{20}H_{31}O_7N_8$ requires N, 15.45%).

1:3-Bis-(*N*-phenyl-4-amidinophenoxy)propane.—Powdered aluminium chloride (2.67 g.; 1 mol.) was added during 10 minutes with stirring to a mixture of 1:3-bis-(4-cyanophenoxy)propane (5.6 g.) and aniline (3.7 g.; 2 mols.) previously heated to 140°, and, after 20 minutes at this temperature, the mixture was cooled and decomposed with hot aqueous alcohol. The crude amidine (6.4 g.) was

liberated and converted into 1:3-bis-(*N*-phenyl-4-amidinophenoxy)propane benzenesulphonate, m. p. 219—220° (Found: N, 7.3. $C_{41}H_{40}O_8N_4S_2$ requires N, 7.2%). The amidine had m. p. 206—207° (Found: N, 12.1. $C_{22}H_{22}O_2N_4$ requires N, 12.1%), and the hydrochloride, m. p. 287—288° (decomp.) (Found: N, 10.5. $C_{22}H_{20}O_2N_4Cl_2$ requires N, 10.4%).

NN-Pentamethylenebenzamidine.—Aluminium chloride (13.4 g.) was added during 20 minutes with cooling in ice-water to phenyl cyanide (10.3 g.) and piperidine (8.5 g.), and the mixture was subsequently heated on the steam-bath for 1½ hours. *NN*-Pentamethylenebenzamidine (6.9 g.), b. p. 98°/0.5 mm., was isolated from the product and converted into the picrate, m. p. and mixed m. p. 173—174° (Part IV).

N-Phenyl-*N*-methylbenzamidine.—Aluminium chloride (6.7 g.) was slowly added to phenyl cyanide (5.15 g.) and methylaniline (5.35 g.), and, after 20 minutes at 160°, *N*-phenyl-*N*-methylbenzamidine (10.5 g.) was isolated; it crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 85.5° (Found: N, 13.3. Calc. for $C_{14}H_{14}N_2$: N, 13.3%). The picrate had m. p. 187° (Found: N, 15.9. Calc. for $C_{20}H_{17}O_7N_5$: N, 15.9%). The m. p.s of the amidine and its picrate are recorded in Part V as 85° and 186—188° respectively.

NN-Diethyl-*p*-methylsulphonylbenzamidine.—A mixture prepared by slowly adding aluminium chloride (7 g.) to *p*-methylsulphonylphenyl cyanide (9.05 g.) and diethylamine (7.3 g.; 2 mols.) was heated on the steam-bath for 1½ hours, and afforded the crude amidine (12.8 g.) as a gum. *NN*-Diethyl-*p*-methylsulphonylbenzamidinium picrate had m. p. 184.5° (Found: N, 14.7. $C_{18}H_{21}O_9N_5S$ requires N, 14.5%), and the toluene-*p*-sulphonate had m. p. 162° (Found: N, 6.6. $C_{19}H_{20}O_8N_5S_2$ requires N, 6.6%).

NN-Pentamethylene-*p*-methylsulphonylbenzamidine.—(a) A mixture of *p*-methylsulphonylphenyl cyanide (9.05 g.), piperidine (8.5 g.; 2 mols.), and aluminium chloride (7 g.), prepared and heated as in the last example, afforded *NN*-pentamethylene-*p*-methylsulphonylbenzamidine (13.1 g.), m. p. 97° (Found: N, 10.4. $C_{13}H_{18}O_2N_2S$ requires N, 10.5%). The picrate was first obtained from methanol in slender needles, m. p. 199—199.5° (Found: N, 14.2. $C_{19}H_{21}O_9N_5S$ requires N, 14.5%), but a second form crystallising from the same solvent in cubic crystals, m. p. 188.5°, was subsequently obtained. The lower-melting form was converted into the needle form, m. p. 199.5°, at its m. p., and either could be obtained by inoculating a methanolic solution with a crystal of the desired form. The toluene-*p*-sulphonate crystallised from alcohol in prisms, m. p. 230—231° (Found: N, 6.5. $C_{20}H_{22}O_8N_5S_2$ requires N, 6.4%).

The following experiments, performed on a 0.025 g.-mol. scale using equimolecular proportions of the reactants, illustrate the influence of solvents on the yield of amidine. The yields are in terms of the picrate, m. p. 199.5°.

Solvent.	Nitrobenzene.	Chloroform.	Carbon tetrachloride.	Benzene.	
Vol., c.c.	20	25	25	25	25
Temp.	95°	65°	80°	85°	85°
Time, hrs.	1	2	2	2	6
Yield, %	25	15.2	25.0	56.5	60.5

(b) Triphenylaluminium, prepared from aluminium turnings (1 g., 2.7 atoms) and diphenylmercury (5 g.; 1 mol.) (cf. Hilpert and Gruttner, *Ber.*, 1912, **45**, 2828), was mixed with *p*-methylsulphonylphenyl cyanide (2.5 g.) and piperidine (1.2 g., 1 mol.). The temperature rose spontaneously to 125° and was maintained by heating for another 10 minutes. The crude amidine (1.7 g.) was isolated, and afforded the pure picrate (2.2 g., 32%), m. p. 199.5°.

(c) A solution of *p*-methylsulphonylphenyl cyanide (3.62 g.), piperidine (1.7 g.; 1 mol.), and triphenyl borate (5.8 g.; 1 mol.) in benzene (10 c.c.) was boiled for 2 hours (internal temp. 85°) and diluted with chloroform, and the amidine was extracted with dilute sulphuric acid. The yield of picrate, m. p. 199.5°, was 3.5%.

(d) The preparation of this amidine by the benzenesulphonate method is described above.

NN-Diphenylpicolinamidine.—2-Cyanopyridine (5.2 g.) and diphenylamine (8.5 g.) were warmed until a homogeneous mixture was obtained, and powdered aluminium chloride (6.7 g.) was then added with stirring, the temperature rising to 85°. The mixture was heated at 140° for 30 minutes and the amidine was then liberated and collected in chloroform. The crude amidine (10.4 g.; m. p. 116—118°) was crystallised several times from light petroleum and afforded *NN*-diphenylpicolinamidine, m. p. 129—130° (Found: N, 15.2. $C_{18}H_{15}N_3$ requires N, 15.4%). The picrate crystallised from methanol in prisms, m. p. 164.5—165.5° (Found: N, 16.5. $C_{24}H_{18}O_7N_5$ requires N, 16.7%).

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[Received, November 27th, 1946.]

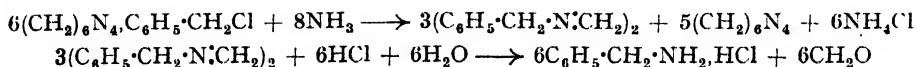
210. The Preparation of Benzylamines from Benzyl Halides and Hexamethylenetetramine.

By JOHN GRAYMORE.

A new method for the preparation of cyclic methyleneimines and thence the corresponding primary amines is described, as is also a method for the preparation of benzylmethylamine. The work also shows that these methyleneimines may be converted into the corresponding aldehydes by heating with hydrochloric acid providing the methyleneimine be in excess.

VARIOUS investigators have described methods for the preparation of primary amines from hexamine-alkyl halides (Delépine, *Compt. rend.*, 1895, **120**, 501; *Bull. Soc. chim.*, 1897, **17**, 290;

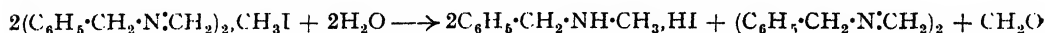
Compt. rend., 1897, **124**, 292; Galat and Elion, *J. Amer. Chem. Soc.*, 1939, **61**, 3585). The present method depends on the preparation of a methyleneimine by decomposition of an aqueous solution of a quaternary compound such as hexamine-benzyl chloride in the presence of excess of ammonia, and subsequent hydrolysis of the cyclic methyleneimine by excess of hydrochloric acid:



Hoch (D.R.-P. 139,394) showed that the oil obtained by adding excess of sodium hydroxide to hexamine-alkyl halides gave a cyclic methyleneimine when gently heated. The cyclic methyleneimine could not, however, be obtained directly by heating an aqueous solution of hexamine-alkyl halide with sodium hydroxide. Heated alone, an aqueous solution of the quaternary compound gives benzaldehyde (Sommelet, *Compt. rend.*, 1913, **157**, 852).

The ammonia serves the double purpose of ensuring the alkalinity of the solution, thus facilitating the polymerisation of the benzylmethyleamine and so preventing its isomerisation to benzylidenemethylamine, and also combines with the liberated formaldehyde.

The hydrochlorides of benzylamine and of *p*-nitro-, *p*-chloro- and *m*-methyl-benzylamine were obtained. The molecular weight (Rast) of the solid methyleneimine, obtained either by the above method or by direct condensation of benzylamine with formaldehyde, indicated it to be a mixture of the dimeride and the trimeride of $\text{CH}_2\cdot\text{N}\cdot\text{CH}_2\text{Ph}$, although it is possible that at the high temperature of melting camphor depolymerisation occurs. Analysis of the addition product of the methyleneimine with methyl iodide also seemed to indicate that the methyleneimine is a mixture. Decomposition of the addition product by heating with water at 80° gave the hydriodide of benzylmethylamine, a benzylmethyleimine, formaldehyde, and a small quantity of a substance apparently the *methiodide* of the trimeride:



The aqueous solution yields benzylmethylamine hydriodide. The method is thus suitable for providing the secondary amine pure and in good yield. The breakdown of quaternary derivatives obtained from the cyclic methyleneimines to give secondary amines has been demonstrated previously (Graymore, *J.*, 1938, 1311) but the above decomposition differs in that the secondary amine is readily recoverable by virtue of the fact that the other products, save formaldehyde, are insoluble in cold water.

It has been shown (Graymore, *J.*, 1945, 293), following a suggestion of Sommelet (*loc. cit.*), that the condensation product of benzylamine with formaldehyde, dissolved in hydrochloric acid, gave benzaldehyde when heated with hexamine. A similar result has now been achieved by heating the condensation product with two-thirds of the quantity of hydrochloric acid as required by the equation $(\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{N}\cdot\text{CH}_2)_2 + 2\text{HCl} = 2\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{N}\cdot\text{CH}_2\cdot\text{HCl}$, the excess of cyclic methyleneimine replacing the hexamine previously used.

EXPERIMENTAL.

Cyclic Benzylmethyleimine.—Hexamine-benzyl chloride (90 g.) was dissolved in water (400 c.c.) containing an excess of ammonia (70 c.c.; *d* 0.88) and the solution heated under reflux (1½ hours). Formaldehyde (20 c.c.; 40%) was now added to remove excess of ammonia and to precipitate any free benzylamine as cyclic methyleneimine. The oily cyclic base was allowed to settle, the greater part of the supernatant liquor decanted, and the residue poured into a large quantity of cold water; solidification of the oil was hastened by vigorous stirring. The solid was then ground, and washed well with cold sodium hydroxide and finally with cold water. The crude product (35–36 g.), *bis*(benzylmethyleimine), recrystallised from cold benzene or light petroleum, had *m. p.* 46° and was identified by comparison with sample prepared directly from benzylamine and formaldehyde [Found: *M* (Rast), 254. $(\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{N}\cdot\text{CH}_2)_2$ requires *M*, 238]. From the decanted liquor, 50 g. of a mixture of hexamine and ammonium chloride were recovered.

Benzylamine hydrochloride. The cyclic imine (10 g., crude), dissolved in excess of concentrated hydrochloric acid, was steam-distilled to remove formaldehyde and traces of benzaldehyde, and evaporated to small bulk; benzylamine hydrochloride crystallised in large plates (11 g.), *m. p.* and mixed *m. p.* 248–249°.

Benzaldehyde from the cyclic base. To the cyclic methyleneimine (10 g.) was added concentrated hydrochloric acid (6 c.c.) and the mixture was gently heated under reflux (1 hr.). The solution was now made strongly acid with dilute hydrochloric acid, refluxed for a minute, and the precipitated benzaldehyde removed by ether and identified; yield 4 c.c. (50%).

Bis-(p-nitrobenzylmethyleimine).—Hexamine-*p*-nitrobenzyl bromide (60 g.) dissolved in water (300 c.c.) containing ammonia (60 c.c.; *d* 0.88), was heated under reflux until the semi-solid orange

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liquid which separated had formed a buff or buff-orange solid (1½ hrs.); this was cooled, removed (yield 23 g.), ground, and recrystallised from hot benzene, forming small needles, m. p. 158°. It dissolved in dilute hydrochloric acid and was reprecipitated as a buff powder. It was slightly soluble in alcohol but very soluble in ethyl acetate [Found: C, 58.5; H, 5.0; N, 16.8; *M* (Rast), 329. $(C_8H_8O_2N_2)_2$ requires C, 58.5; H, 4.9; N, 17.07%; *M*, 328].

(i) This dimer (14 g.) was dissolved in excess of hydrochloric acid (20 c.c., *d* 1.19, in 200 c.c. of water). Steam-distillation removed most of the formaldehyde, and the solution on concentration yielded *p*-nitrobenzylamine hydrochloride in yellow crystals (15 g., crude). Most of the yellow colour was extracted by washing with a small quantity of warm alcohol, and recrystallisation from water afforded needles decomposing at 256° (Found: Cl, 18.8. Calc. for $C_7H_8O_2N_2 \cdot HCl$: Cl, 18.8%).

(ii) To the cyclic methyleneimine (6 g.) was added hydrochloric acid (*d* 1.19; 2.6 c.c.) and the mixture was gently refluxed (½ hr.). After addition of an excess of dilute hydrochloric acid with cooling, *p*-nitrobenzaldehyde separated (0.8 g.); a further quantity was obtained on dilution of the filtrate with water. Recrystallised from hot water, it was obtained as a pale yellow substance, m. p. 106°, identified by conversion into its 2:4-dinitrophenylhydrazones.

Decomposition of Hexamine-p-Chlorobenzyl Chloride.—The quaternary compound (30 g.), dissolved in water (100 c.c.) containing ammonia (*d* 0.88; 30 c.c.), was heated under reflux (1 hr.). After cooling, the supernatant liquor was decanted from the oily methyleneimine, the latter washed several times with water, extracted with ether, and dried over solid sodium hydroxide. After removal of the ether, the base *p*-chlorobenzylmethyleneimine was distilled under reduced pressure and obtained as a viscous oil, b. p. 220°/100 mm. (Found: C, 62.5; H, 5.21. C_8H_8NCl requires C, 62.6; H, 5.2%). The molecular weight was not determined.

(i) This imine (6 g.) was dissolved in excess of hydrochloric acid, steam-distilled to remove formaldehyde, and evaporated to small bulk, *p*-chlorobenzylamine hydrochloride crystallising out on cooling; recrystallised from alcohol, it melted at 250° (6 g.) (Found: N, 7.9. Calc. for $C_7H_8NCl \cdot HCl$: N, 7.9%).

(ii) To the imine (6 g.) was added hydrochloric acid (*d* 1.19; 3 c.c.), and the mixture was heated gently under reflux (10 mins.). Excess of hydrochloric acid was now added, and boiling continued for 5 mins. On cooling, *p*-chlorobenzaldehyde separated as an oil which was extracted with ether. On removal of the ether it solidified (yield 2.5 g.). It was identified by oxidation to *p*-chlorobenzoic acid, m. p. and mixed m. p. 236°.

m-Methylbenzylamine Hydrochloride.—To hexamine-*m*-methylbenzyl bromide (25 g.), dissolved in water (100 c.c.), was added ammonia (*d* 0.88; 30 c.c.), and the solution heated under reflux (1 hr.). The syrupy oil which separated was removed, washed with cold water, dissolved in excess of hydrochloric acid, steam-distilled to remove formaldehyde, and the solution concentrated. *m*-Methylbenzylamine hydrochloride separated, and recrystallised from water in needles (7 g.) (Found: Cl, 22.5. Calc. for $C_8H_{12}NCl$: Cl, 22.5%).

cycloHexylmethyleneimine.—Addition of cyclohexylamine (50 g.) slowly to formaldehyde (40 c.c., 40%) precipitated an oil which solidified. From alcohol it crystallised in long prisms, m. p. 75° (Found: C, 75.1; H, 11.7; N, 12.7; *M* (Rast), 144. $C_6H_{13}N$ requires C, 75.6; H, 11.7; N, 12.6%; *M*, 111. $C_6H_{11}N \cdot CH_2$ requires *M*, 111).

Benzylmethyleneimine Methiodide.—To benzylmethyleneimine [1 mol. calculated as $(C_6H_5 \cdot CH_2 \cdot N \cdot CH_2)_3$], recrystallised from light petroleum and dissolved in dry ether, was added methyl iodide (1½ mols.). After one day the precipitated methiodide was filtered off [Found: C, 59.1; H, 5.32; N, 8.1; I, 27.4. $(C_6H_5 \cdot CH_2 \cdot N \cdot CH_2)_3 \cdot CH_3I$ requires C, 53.7; H, 5.5; N, 7.37; I, 33.4%. $(C_6H_5 \cdot CH_2 \cdot N \cdot CH_2)_3 \cdot CH_3I$ requires C, 60.1; H, 6.0; N, 8.4; I, 25.5%].

Hydrolysis of Cyclic Benzylmethyleneimine Methiodide: Preparation of Benzylmethylamine Hydroiodide.—The foregoing addition compound (18 g.) was suspended in water (250 c.c.) in an open vessel and heated at 70–80° for one hour. The methiodide slowly decomposed, a sticky oil was deposited, and formaldehyde was evolved. On cooling, the oil partly solidified and a small quantity of a white solid (A, see below) separated in needles (slightly soluble in hot water). The filtrate was evaporated on the water-bath to dryness, formaldehyde being evolved, and gave benzylmethylamine hydroiodide in yellow needles (9 g., crude). Crystallised from hot alcohol (twice), it formed white needles, m. p. 164° (Emde, *Arch. Pharm.*, 1909, **247**, 364, gives m. p. 124°) (Found: C, 38.7; H, 4.8; N, 5.3; I, 51.2. Calc. for $C_8H_{12}NI$: C, 38.6; H, 4.8; N, 5.6; I, 51.0%). It was further identified by conversion into *p*-toluenesulphonbenzylmethylamide, m. p. 92–93° (Found: S, 11.4. Calc. for $C_{11}H_{11}O_2NS$: S, 11.6%). The residue (A, above) was ground, and extracted with ether. The ethereal solution yielded cyclic benzylmethyleneimine, m. p. 46° (4 g.) [Found: C, 80.6; H, 7.6; *M* (Rast), 242. Calc. for $(C_6H_5N)_2$: C, 80.6; H, 7.6%; *M*, 238]. The residue from the ethereal extract recrystallised from hot alcohol in needles, m. p. 160–161°, of the methiodide of tris(benzylmethyleneimine) (4 g.) (Found: I, 25.3; N, 8.17. $C_{23}H_{30}N_3I$ requires I, 25.5; N, 8.4%). Heated with water at 80°, it decomposed slowly to give benzylmethylamine hydroiodide, formaldehyde, and cyclic benzylmethyleneimine. At higher temperatures under reflux a small quantity of benzaldehyde is formed.

Analysis and molecular-weight determinations were by Drs. Weiler and Strauss.

211. The Kinetics of the Reaction between Copper and Iodine in Various Solutions. Part II. Solutions of Iodine in Organic Solvents.

By L. L. BIRCUMSHAW and M. H. EVERDELL.

The kinetics of the reaction between copper and iodine when dissolved in carbon tetrachloride, chloroform, benzene, or diamyl ether has been investigated. In carbon tetrachloride and chloroform the rate appears to follow the equation $dx/dt = k(a - x)/x$, where the symbols have their usual significance. The influence of the state of the surface of the copper and the temperature coefficient has also been studied. Whereas in the work (Part I) on aqueous (potassium iodide) solutions of iodine it was shown for a large range of iodine concentrations that the rate of reaction is unaffected by the presence or thickness of the film of cuprous iodide, yet with the above solutions the rate appears to be partly controlled by the thickness of the iodide film.

IN Part I (*J.*, 1942, 598) the results of a study of the rate of reaction of copper on iodine in aqueous (potassium iodide) solution were communicated. It was shown that for a large range of iodine concentration the reaction was unimolecular with respect to the iodine concentration, and the rate was unaffected by the presence or absence of a cuprous iodide film or by the method of preparation or degree of smoothness of the copper surface. The increase in reaction rate found on increasing the potassium iodide concentrations to very high values was identified with the increase in the rate of diffusion of iodine in these circumstances. It was also demonstrated that the reaction proceeds by the diffusion of both iodine and solvent through the cuprous iodide film and not by the diffusion of copper ions.

It is well known that iodine dissolved in aqueous potassium iodide is present largely in the form of the complex ion I_3^- , the proportion of free iodine molecules being very small. In the case of organic solvents giving violet solutions the iodine is considered to exist as simple molecules, whereas in the brown solutions obtained with ethers, ketones, or esters it exists mainly as a co-ordination complex with the solvent. The great difference in the state of the iodine in aqueous solutions on the one hand, and in organic solvents on the other, might be expected to have a considerable effect on the kinetics of the reaction between copper and iodine, and it was decided to extend the work to solutions of the latter type.

This work may be divided into the following sections: (1) Experiments carried out between copper and iodine in carbon tetrachloride solution at 25°. The initial concentration of the solutions varied from 0.0025 to 0.04 g.-atom/l. (2) Experiments at 25° in chloroform, benzene, and diamyl ether, showing the effect of change of solvent. (3) Experiments at 0°, 25°, and 30°, showing the effect of change of temperature. (4) Experiments at 25°, showing the influence of the state of the copper surface on the rate of reaction.

EXPERIMENTAL.

The experimental method has been described (Part I, *loc. cit.*). Briefly it consisted in rotating strips of thick copper foil of 36 sq. cm. area in the iodine solution at about 100 revs./min. The course of the reaction was followed by titration: 5 c.c. of the solution were pipetted into an excess of N/1600-sodium thiosulphate solution, shaken until all the iodine had reacted, and then back-titrated with N/1600-iodine solution. The copper strips showed a firm film of whitish-brown cuprous iodide which exhibited no crumbling.

Carbon tetrachloride. "AnalaR" Carbon tetrachloride was distilled over calcium chloride and then repeatedly over clean, polished strips of copper to remove any traces of sulphur present. Fractions boiling at 76.7° were used for the work. The results are given in Table I, where $k = \frac{2.303v}{t_2 - t_1} \log_{10} \frac{C_1}{C_2}$ and x is given in g.-atoms $\times 10^6$, all the data relating to 25°.

Col. 7 in the readings for initial concentration N/400, contains the values of the simple unimolecular constant k (corrected for the volume change). In the reaction for copper with iodine in aqueous (KI) solution a constant is given by this equation, but in the present experiments it is seen that k falls rapidly with time. This suggests that the reaction is retarded by the cuprous iodide film. However, that the Tammann-Pilling-Bedworth equation $x^2 = kt$ is not obeyed is seen by an examination of Fig. 1, where x is plotted against time. If this relation were obeyed, values of x for a particular time t should all be equal and independent of the initial concentration of the iodine. It can also be seen that the ordinates are not proportional to the iodine concentration, which should be the case if the unimolecular relation is obeyed. It appeared probable that this reaction in organic media (a) was proportional to the iodine concentration, and (b) was inversely proportional to the thickness of the cuprous iodide film formed on the copper. Hence, if a = initial concentration of iodine and $a - x$ = concentration of iodine at time t ,

$$dx/dt = k(a - x)/x \quad \dots \dots \dots (1)$$

since x is proportional to the thickness of the cuprous iodide film. The integrated form of this equation, giving k , the velocity constant, will only hold for the reaction at constant volume. In the present work

TABLE I.

Time, mins.	(a - x).	[I], C.	x.	χ .	k_n .	k .
300 C.c. of N/400-iodine in CCl ₄ .						
0	20.0	0.0025	—	—	—	—
10	17.5	0.00219	2.5	2.60	0.192	4.01
20	16.2	0.00202	3.8	3.94	0.265	2.28
30	15.5	0.00194	4.5	4.64	0.193	1.28
60	13.9	0.00174	6.1	5.52	0.196	1.03
90	12.65	0.00158	7.35	6.73	0.206	0.88
150	11.15	0.00139	8.85	8.17	0.161	0.58
					Mean 0.202	

Time, mins.	(a - x).	[I], C.	x.	χ .	k_n .	Time, mins.	(a - x).	[I], C.	x.	χ .	k_n .
300 C.c. of N/200-iodine in CCl ₄ .						300 C.c. of N/50-iodine in CCl ₄ .					
0	20.0	0.005	—	—	—	0	20.0	0.020	—	—	—
10	18.2	0.0045	1.8	3.75	0.194	10	19.2	0.0192	0.8	6.67	0.150
20	17.65	0.00441	2.35	4.877	0.140	25	18.7	0.0187	1.3	10.77	0.162
30	17.15	0.00429	2.85	5.884	0.134	50	18.15	0.0181	1.85	15.2	0.165
60	16.1	0.00402	3.9	7.962	0.149	100	17.35	0.0173	2.65	21.5	0.170
120	14.3	0.00357	5.7	11.462	0.193	160	16.7	0.0167	3.3	16.6	0.187
180	12.9	0.00322	7.1	14.135	0.217	250	16.0	0.0160	4.0	31.9	0.162
Mean 0.171						390	15.0	0.0150	5.0	39.4	0.183
						Mean 0.169					

300 C.c. of N/100-iodine in CCl ₄ .						300 C.c. of N/25-iodine in CCl ₄ .					
0	20.0	0.01	—	—	—	0	20.0	0.040	—	—	—
10	18.75	0.00937	1.25	5.25	0.185	8	19.5	0.0390	0.5	8.33	0.144
20	18.25	0.00912	1.75	7.26	0.181	40	18.8	0.0376	1.2	19.8	0.172
30	17.85	0.00892	2.15	8.69	0.174	80	18.3	0.0366	1.7	17.9	0.167
60	16.95	0.00847	3.05	12.51	0.196	140	17.7	0.0354	2.3	36.0	0.186
120	15.6	0.00780	4.4	17.60	0.205	220	17.1	0.0342	2.9	45.3	0.183
180	14.5	0.00725	5.5	21.80	0.197	Mean 0.170					
270	13.4	0.00670	6.6	25.93	0.193						
390	12.3	0.00615	7.7	29.97	0.179						
600	10.8	0.00540	9.2	35.39	0.177						
Mean 0.187											

the volume of the reacting liquid varies with each reading owing to the extraction of 5.0 c.c. for the titration. The immediate problem is to insert this volume correction into equation (1).

If m is the mass of iodine in solution, and c and v are the concentration and volume respectively, then $m = cv$ and

$$-dm/dt = -d(cv)/dt$$

If c_0 = initial concentration and v_0 = initial volume then

$$-d(cv_0)/dt = kc/v_0(c_0 - c)$$

because $v_0(c_0 - c)$ is proportional to the thickness of the cuprous iodide film at any moment during the first interval; hence

$$k_1 = \frac{v_0^2}{t_1 - t_0} (c_0 \ln \frac{c_0}{c_1} - c_0 + c_1) \quad (2)$$

At t_1 , we remove 5 c.c., and with the new volume v_1 we have

$$-v_1 \frac{dc}{dt} = \frac{kc}{v_0(c_0 - c_1) + v_1(c_1 - c)}$$

because $v_0(c_0 - c_1)$, now constant, represents the thickness of the film at the beginning of the second interval. Additional amounts of iodine added during the second stage are represented by $v_1(c_1 - c)$. Integrating between the limits c_1 and c_2 and t_1 and t_2 , we have

$$k_2 = \frac{v_1 v_0 (c_0 - c_1) \ln (c_1/c_2) + v_1^2 c_1 \ln (c_1/c_2) - v_1^2 (c_1 - c_2)}{t_2 - t_1} \quad (3)$$

This equation gives k_2 , the velocity constant for the second interval. Similarly for the third interval we have

$$-v_2 \frac{dc}{dt} = \frac{kc}{v_0(c_0 - c_1) + v_1(c_1 - c_2) + v_2(c_2 - c)}$$

which, integrated between the limits t_2 and t_3 and c_2 and c_3 , gives

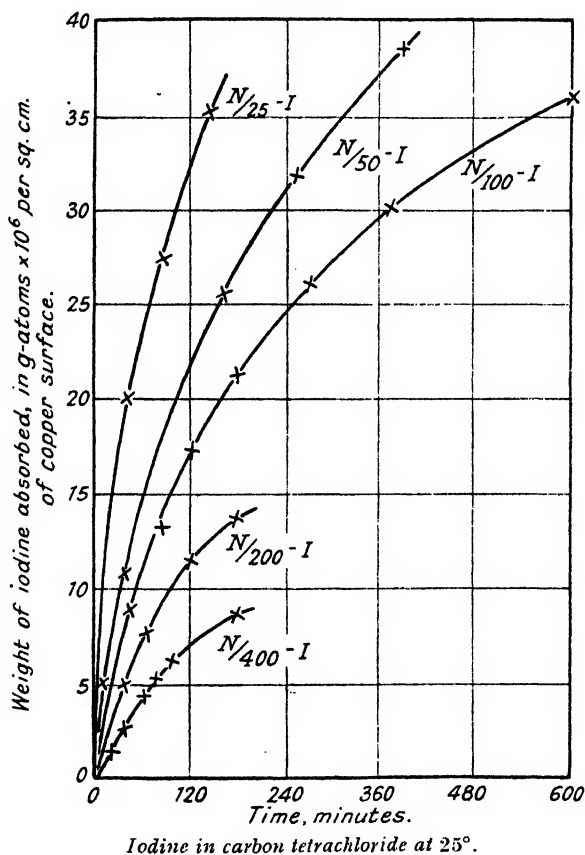
$$k_3 = \frac{v_2 \{v_0(c_0 - c_1) + v_1(c_1 - c_2)\} \ln (c_2/c_3) + v_2^2 c_2 \ln (c_2/c_3) - v_2^2 (c_2 - c_3)}{t_3 - t_2} \quad (4)$$

the velocity constant for the third interval. For the n th interval we have,

$$k_n = \frac{v_{n-1}\{v_0(c_0 - c_1) + v_1(c_1 - c_2) + \dots + v_{n-2}(c_{n-2} - c_{n-1})\} \ln(c_{n-1}/c_n) + v_{n-1}^2 c_{n-1} \ln(c_{n-1}/c_n) - v_{n-1}^2 (c_{n-1} - c_n)}{t_n - t_{n-1}} \quad (5)$$

From equation (5) we can calculate k for any interval (corrected for the change of volume). It is noteworthy that if equation (2) is used for all intervals in the reaction the differences shown in the values of the constant so obtained are small, *i.e.*, the correction term for the change of volume is small. That equation (5) is similar to equation (2), save for the inclusion of the volume changes in (5), may be shown by putting $v_1 = v_2 = v_3 \dots = v_n$ in equation (5), whereupon it reduces to equation (2). The values of k_n are given in Table I. They are fairly constant, but the agreement is not excellent. When the average values are compared for different initial concentrations of iodine they show no regular drift.

FIG. 1.



Iodine in carbon tetrachloride at 25°.

A direct contrast between the reaction in aqueous potassium iodide and that in carbon tetrachloride can therefore be made. In the former case the reaction appears to be independent of the presence or thickness of the cuprous iodide film, whereas in the latter case the reaction is directly controlled by the film thickness.

The Effect of the Solvent on the Reaction Rate.—In the determination of the effect of the solvent on the rate four organic liquids have been used.

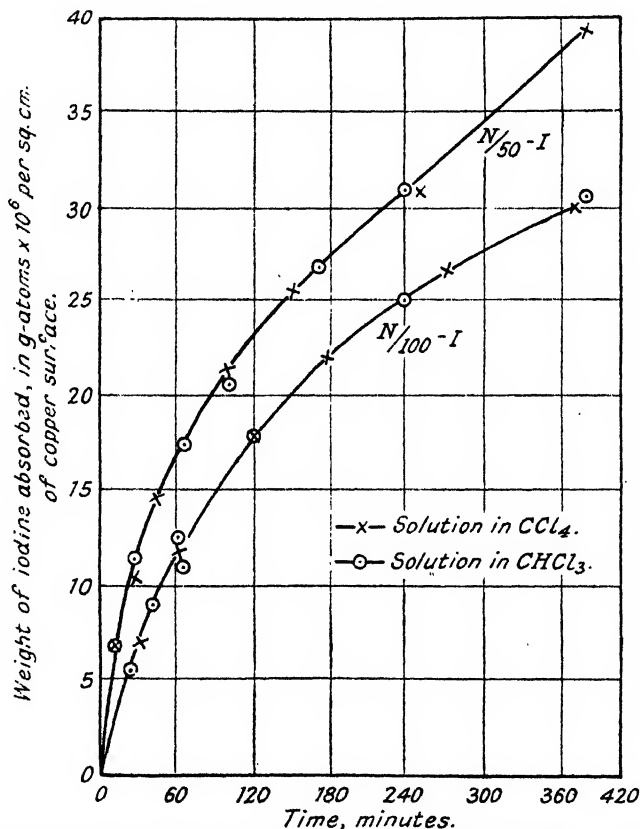
"AnalaR" Chloroform containing no foreign matter detectable by analysis (free acid, Cl^- , Cl_2 , CHO , COCl_2) was kept over calcium chloride for 36 hours, decanted, and distilled. The first fractions were discarded, and the bulk of the liquid, b. p. 60.2°, reserved for the experiments. Data were obtained for two concentrations of iodine, $N/100$ and $N/50$. The results are shown in Fig. 2, and it is seen that the rates in carbon tetrachloride and in chloroform are practically identical.

"AnalaR" Benzene containing 0.001% of thiophen and 0.002% of non-volatile matter was kept over copper foil for several days and then over fused calcium chloride. After decantation the liquid was distilled, and further purified by freezing. The m. p. of the final fraction was 5.5°, and this was used for the work. The copper surface was prepared by carborundum straight polishing (Part I, *loc. cit.*). Preliminary experiments showed that the rate in benzene is less than in carbon tetrachloride,

so experiments were carried out over a range of concentration $N/400$ — $N/25$. The results are shown graphically in Fig. 3, and it is seen that for concentrations greater than and including $N/100$ the rate of reaction in benzene is less than that in carbon tetrachloride; moreover, the difference in rate for the same concentration in the different solvents increases with increasing concentration. For solutions of $N/200$ -iodine the rate in benzene is slightly greater than in carbon tetrachloride, and this difference is more pronounced in the case of $N/400$ -solutions.

The solutions of iodine in certain oxygen-containing organic liquids, *e.g.*, ethers, esters, and ketones, show a deep brown colour when concentrated, changing to red at high dilutions. It is usually supposed that in such solutions co-ordination compounds exist between iodine and the solvent, the oxygen in the solvent acting as a donor element. It was desired to use such a solvent for this reaction. Of the common esters, ethers, and ketones, none is suitable. Acetone, which reacts with iodine in the presence of traces of alkali, was considered unsafe; diethyl ether and ethyl acetate have relatively high vapour pressures at 25° , and with the apparatus used, evaporation troubles would be encountered. The liquid

FIG. 2.



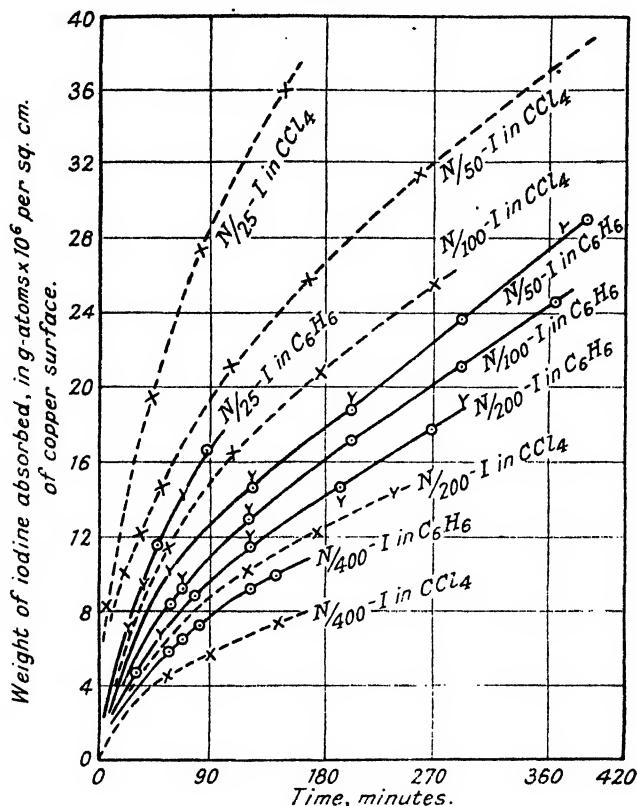
Comparison of reaction rates in chloroform and carbon tetrachloride at 25° .

eventually selected was diamyl ether. This, except for the reversible complex formation, is without action on iodine. Diamyl ether, obtained in large quantities, was purified by standing over calcium chloride, then copper foil, and by repeated distillation. The fraction of b. p. 168° was reserved for the experiments. It was intended to follow the course of the reaction in the usual way, *i.e.*, by titration, but this was found to be impossible, for the iodine in diamyl ether appears to react very slowly with sodium thiosulphate solution (possibly the dissociation of the iodine complex is very slow). On this account the rate was investigated gravimetrically. Copper strips were cut, polished, dried, and weighed. After reaction, the strip with the cuprous iodide film was washed well with diamyl ether, dried, and weighed again. The difference in weight gives the amount absorbed by the copper as cuprous iodide in time t . A new sheet of copper and a new solution of iodine were used for each experiment. The results are given in Table II, and the increases in weight are the means of two identical experiments; the iodine absorbed (col. 5) is given in terms of g-atoms $\times 10^6$ per sq. cm. of surface. The strips could be very accurately cut, and the slight variations in weight are due to slight variations in thickness. It can be seen that at all concentrations the rate in diamyl ether is much less than the rate in carbon tetrachloride.

Effect of Temperature.—The temperature coefficient of the reaction between copper and iodine in aqueous (potassium iodide) solution is small, but large enough to permit accurate measurement of the change of rate due to 5° increase to be taken. It was intended to study the reaction in organic solvents

at 20°, 25°, 30° and 35°. Preliminary experiments showed, however, that the rate of reaction at 30° was very little greater than at 25°. The increase was too small to be shown accurately, and as it was undesirable to work at temperatures much above 25° it was decided to work at 0°. In this case, extreme

FIG. 3.



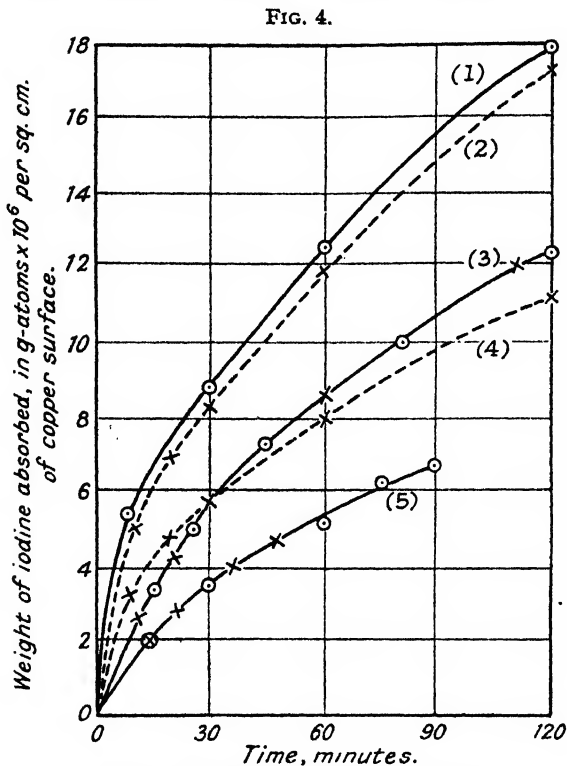
Comparison between rates of reaction in benzene and carbon tetrachloride at 25°.

TABLE II.

Time, mins.	Initl. wt. of Cu, g.	Wt. of Cu + Cu ₂ I ₂ , g.	Increase, g.	I absorbed.	Time, mins.	Initl. wt. of Cu, g.	Wt. of Cu + Cu ₂ I ₂ , g.	Increase, g.	I absorbed.
N/50-Iodine.									
15	4.1900	4.2069	0.0169	3.696	60	4.1802	4.2110	0.0308	6.736
30	4.1580	4.1810	0.0230	5.031	75	4.1905	4.2240	0.0335	7.326
45	4.1827	4.2101	0.0274	5.992	90	4.1852	4.2210	0.0358	7.830
N/200-Iodine.									
15	4.1906	4.2022	0.0116	2.537	75	4.2134	4.2386	0.0252	5.511
30	4.3256	4.3425	0.0169	3.696	90	4.2616	4.2890	0.0274	5.992
45	4.2016	4.2217	0.0201	4.396	105	4.1558	4.1850	0.0292	6.386
60	4.1724	4.1950	0.0226	4.942	120	4.0154	4.1372	0.0318	6.955
N/100-Iodine.									
15	4.2044	4.2200	0.0156	3.441	75	4.1606	4.1897	0.0291	6.364
30	4.0996	4.1185	0.0195	4.264	90	4.1324	4.1636	0.0312	6.823
45	4.1678	4.1915	0.0237	5.183	105	4.1564	4.1906	0.0342	7.480
60	4.2110	4.2376	0.0266	5.817	120	4.1888	4.2258	0.0370	8.092

care was taken to ensure the sealing of the reaction vessel, since at 0° the introduction of air would lead to water-vapour condensation. The temperature coefficient was investigated in this way with carbon tetrachloride and chloroform. The results are shown in Fig. 4, and it will be seen that the coefficient is very small.

Effect of Surface Condition of the Copper on the Rate.—The presence of an oxide film or different methods of preparing the surface of the metal have no effect on the rate of reaction in aqueous (KI) solution. It has been shown also that the rate of reaction in such solutions under the conditions studied is independent of the presence or thickness of the cuprous iodide layer on the copper. For reactions in carbon tetrachloride and chloroform it has been shown that the reaction is controlled by diffusion through the cuprous iodide layer. The structure of the film might well be influenced by the condition of the surface of the copper. It was therefore decided to investigate the effect of the condition of the surface on the rate.



Effect of temperature on rate of reaction.

- | | |
|---|---|
| (1) N/100-I in CCl ₄ at 30°. | (4) N/200-I in CCl ₄ at 25°. |
| (2) N/100-I in CCl ₄ at 25°. | (5) N/200-I at 0°: { × CCl ₄ , ○ CHCl ₃ . |
| (3) N/100-I at 0°: { × in CCl ₄ , ○ in CHCl ₃ . | |

The four different methods of preparing the surface have been described in Part I (*loc. cit.*), i.e., (i) carborundum straight polishing, (ii) carborundum circular polishing, (iii) mirror finish with jeweller's rouge, (iv) etching with dilute nitric acid.

These experiments were all carried out in benzene solution, as it was considered that the films in benzene appeared rather more even and less liable to flaking than in other solvents. The results are shown in Fig. 5. Only slight differences could be detected, but it can be seen that: (1) The rates in the case of carborundum straight and carborundum circular polishing are identical; (2) the rate on the mirror surface is slightly less, (3) the acid-etched surface gives an even lower reaction rate. That is, the rate is less with the smooth surfaces, coarseness of abrasion tending to increase the velocity of the reaction.

The presence of an oxide film on the copper. Copper strips of the correct area were polished by carborundum straight polishing and heated to 100° for 30, 20, and 10 mins. as described in Part I. The oxidised copper was placed in the reaction vessel, and the reaction followed in the usual way by titration. The results are shown in Fig. 6, and it will be seen that the rate in both carbon tetrachloride and benzene is considerably decreased by the presence of an oxide film.

Films formed in Aqueous and Organic Solvents.—It has been shown that for a large range of iodine concentrations the rate of reaction in aqueous solution is unaffected by the presence or thickness of the cuprous iodide film on the copper, whereas in the case of reactions carried out in organic solvents this film controls the reaction. The question arises as to whether this difference is due to a difference in the actual films formed in the two cases or to the nature of the solutions in the two different classes of solvent.

Strips of copper foil of the usual size were polished and then rotated in a solution of N/200-iodine in N/50-potassium iodide for 30 minutes. The strips of copper covered with cuprous iodide film were then removed from the solution and washed and dried carefully. Some of the strips showed small cracks in

FIG. 5.

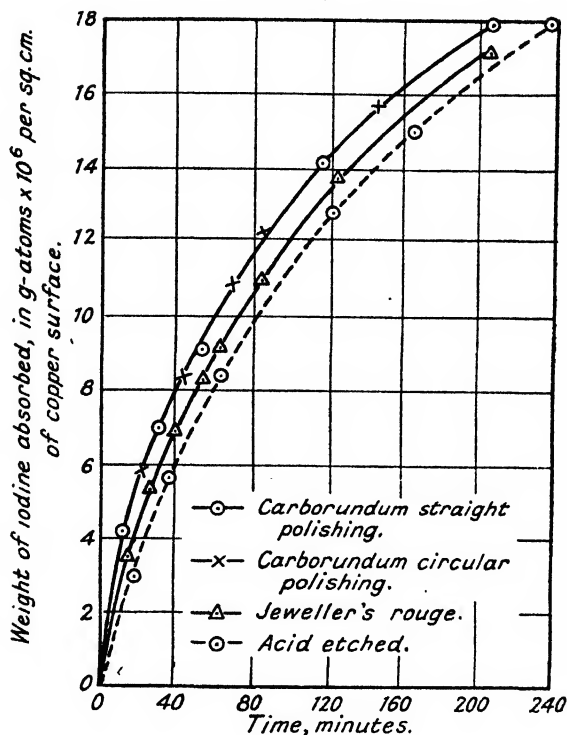
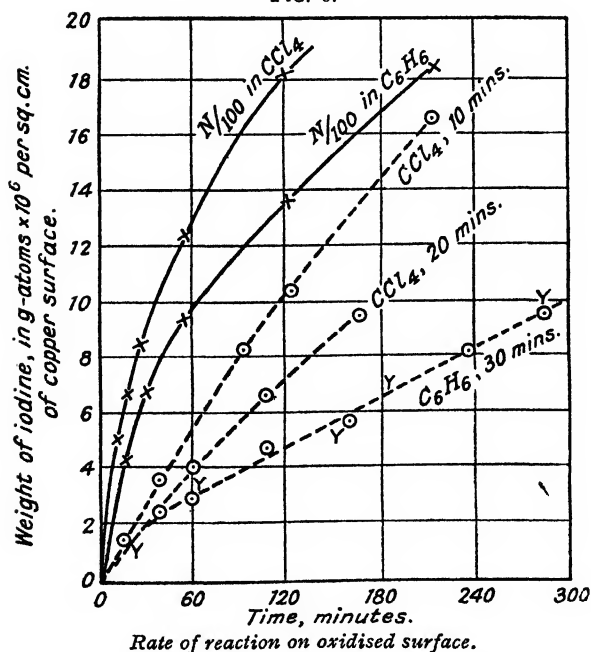


FIG. 6.



the films on drying and these were discarded. The "perfect" strips were then rotated in carbon tetrachloride, and the reaction followed by titration in the usual way. The results are given in Table III, (1) and (2), where χ is expressed as g-atoms of I $\times 10^6$.

TABLE III.

(1) *Copper covered by cuprous iodide film formed in aqueous solution rotated in N/200-iodine in carbon tetrachloride at 25°.*

Time, mins.	10	20	30	60	120	180
x_0	0.83	1.45	1.85	3.04	5.57	7.48
x (no previous film)	3.75	4.88	5.88	7.96	11.46	14.135

(2) *Copper covered by cuprous iodide film formed in carbon tetrachloride solution rotated in N/200-iodine solution at 25°.*

Time, mins.	2	5	10	15	20	30	40	50	60
x_0	1.67	4.33	8.56	12.12	15.43	20.58	24.71	27.65	30.00
x (no previous film)	1.87	4.54	8.57	12.13	15.43	20.78	24.91	28.04	30.38

The results described under (1) were not very reproducible owing to a certain amount of film-cracking, but they clearly showed that the rate in carbon tetrachloride solution is much decreased by the presence on the metal of a film deposited from an aqueous solution. The results described under (2) were easily reproducible and it is seen that the rate is unaffected by the presence of a cuprous iodide film formed in carbon tetrachloride.

DISCUSSION.

The actual rate of reaction observed in these experiments probably depends ultimately on the collisions of the iodine molecules on the copper surface, whatever the means by which the iodine travels through the cuprous iodide film. The rate of diffusion of the iodine molecules through the film will be a function of the concentration gradient of the molecules across the film, *i.e.*, the concentration of an adsorbed film of iodine on the liquid side of the cuprous iodide and the concentration, much lower, of iodine at the film (Cu_2I_2)-metal interface. The concentration of the adsorbed film of iodine will obviously depend on the state of the iodine in solution. Lachmann (*J. Amer. Chem. Soc.*, 1903, 25, 50), after an examination of iodine solutions in 60 organic solvents, distinguished two types of solution: (1) violet solutions from substances like carbon tetrachloride, chloroform, etc. (substances called saturated by Lachmann); (2) brown solutions from ethers, esters, alcohols, and ketones (substances called unsaturated by him). This subject has been investigated by a number of workers but on the whole there seems to be little doubt that Lachmann's original classification was correct.

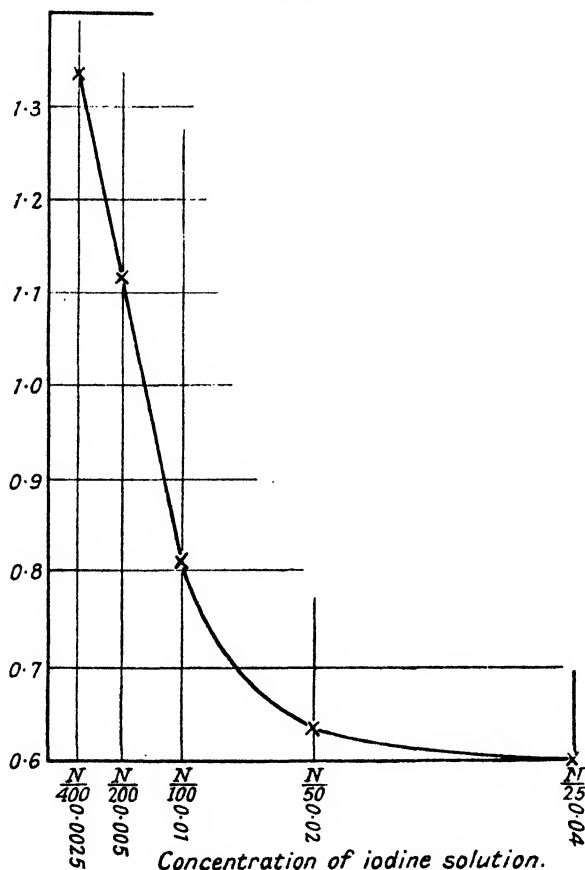
The problem of the benzene solution of iodine is not so simple, and on the collected evidence as a whole these solutions seem to fall directly into neither class. The problem has been investigated in recent years by Walker (*Trans. Faraday Soc.*, 1935, 31, 1432). This solution was placed by both Lachmann and by Getman (*J. Amer. Chem. Soc.*, 1928, 50, 2883) in the violet group, yet the colour is definitely reddish and very different from that in carbon tetrachloride, especially in concentrated solution: in more dilute solution the colours are more alike. From a study of the absorption spectrum, Walker concluded that there was some interaction between iodine and benzene. Hildebrand and Jenks (*ibid.*, 1920, 42, 2180) also showed that benzene solutions of iodine are abnormal with respect to their solubility-temperature relationships compared with other violet solutions. The problem of the possible solvation of iodine in benzene solution is made more complex by the fact that the resulting dipole moment is zero; yet when the evidence as a whole is considered some type of interaction seems to be indicated.

Some simple experiments made by the authors are not without significance. The solutions in carbon tetrachloride or chloroform can be titrated readily with sodium thiosulphate, the end-point being reached with no period of delay; but if 20 c.c. of an N/100-iodine solution in diamyl ether are titrated with N/100-thiosulphate in the presence of starch, the blue colour fades after the addition of a few c.c. of titrant. After about one hour's standing the colour returns, but is again dispersed by the addition of a small amount of thiosulphate, returning again after standing. The theoretical volume of thiosulphate solution required for titration is reached only after several days. This suggests that the thiosulphate only reacts with the free iodine, and that the restoration of the equilibrium between the latter and the complex is slow. If with benzene a solvent-iodine complex is formed in the same way and the complex is of the same nature, the same difficulty might be expected in direct titrations. No such difficulty is experienced, however, so that, although iodine and benzene may form some sort of complex, it is not of necessity of the same type or of the same degree of stability as those formed in the brown solutions.

It is seen in Fig. 2 that the rates of reaction in carbon tetrachloride and chloroform are identical. This is in agreement with Evans and Bannister's results (*Proc. Roy. Soc.*, 1929, A, 125, 370) for the reaction between silver and iodine: it might be expected, since the state of

iodine in the two solvents is believed to be the same, *i.e.*, simple molecules. Table II shows that the rate in diamyl ether is much less than the rates in carbon tetrachloride at the same concentration. This might be due to any of the following causes: (1) Only the free iodine molecules diffuse through the cuprous iodide film and react with the metal. (2) Both the free iodine molecules and the complex molecules diffuse through the film but only the free iodine molecules react. (3) Both the free iodine molecules and the complex may react with the copper, but the passage of the complex through the cuprous oxide layer will almost certainly be much slower, owing to its large molecular size.

FIG. 7.



Ratio between ordinates for benzene to ordinates for carbon tetrachloride.

Fig. 3 shows the rate of reaction in benzene compared with the rate in carbon tetrachloride at the same concentrations. Consider first the experiments at concentrations 0.01, 0.02, and 0.04N. The rate of reaction is less than in carbon tetrachloride and the difference increases with increase of iodine concentration. However, the rate of 0.0025N-iodine in benzene is slightly greater than the rate at the same concentration in carbon tetrachloride. If, in Fig. 3, the ordinates of the graph of the reaction in 0.04N-iodine in benzene are compared with those of the graph of 0.04N-iodine in carbon tetrachloride, a fairly constant value of the ratio is obtained; *e.g.*, at time 390, 300, 210, 150, and 60 minutes this ratio is 0.60, 0.61, 0.60, 0.61, and 0.60, respectively. This is, of course, a perfectly arbitrary method of comparing the reaction rates. The average values of this ratio for all the concentrations are plotted against concentration and given in Fig. 7, and show the effect of concentration on the difference in reaction rate in the two solvents. Above concentrations of approximately $N/200$ the rate in benzene is less than that in carbon tetrachloride; below $N/200$ it is greater. It is difficult to see any obvious explanation of this inversion.

Graphs for results at 0°, 25°, and 30° are shown in Fig. 4 and it is seen that the temperature coefficient is very small, much less than in the aqueous solutions.

Unlike the reaction in aqueous solution, in organic liquids the rate is affected by the nature of the metal surface; in general, coarseness of surface tends to increase the rate of reaction. The rate of reaction in both benzene and carbon tetrachloride is decreased by the presence of an oxide film, the degree of reduction increasing with the period of oxidation.

Measurements of the rate in carbon tetrachloride of specimens covered with a cuprous iodide film deposited from aqueous solution showed that the rate was much lower than that obtained with a clean metal surface. Conversely, the rate in aqueous solution of a copper specimen covered with a film deposited from a carbon tetrachloride solution was the same as with the new metal specimen. Clearly, the difference is not due to a difference in the structure of the film deposited from the two types of liquid, aqueous and organic.

When the kinetics of this reaction in aqueous and organic solutions are compared, interest centres round the fact that in aqueous solutions the rate is unaffected by the film, whereas in organic solutions the film appears to control the reaction. It is necessary to explain this difference, which cannot be traced, as we have seen, to differences in the structure of the films of cuprous iodide formed in the two cases. It has been stated (Part I) that in reactions in aqueous solution both solvent and solute are believed to pass through the iodide film. It is possible, however, that in organic solvents these do not enter the film but only the solute diffuses through the iodide. These films are readily wetted by water, but on the other hand, it was found that when a sheet of copper was removed from an organic solution of iodine and the surface liquid drained off the film appeared dry and the weight did not decrease with time as might be expected if the liquid were in the pores of the film and hence evaporated slowly. Attempts were made to remove a portion of a film, to support it on a small stand made from thin glass rod, and touch its upper surface with a drop of carbon tetrachloride. The spreading of the liquid on the solid did not take place rapidly, and for some time the under side of the film showed no signs of the liquid soaking through. Owing to cracks formed in the films, they always collapsed after about a minute, so little reliable evidence was obtained. Some evidence for the fact that organic solvents do not enter the iodide film is obtained from a consideration of the reaction in different organic solvents. If the reaction proceeds by the passage of iodine and solvent through the film, then it might be supposed that in using organic solvents of different viscosities different rates might be obtained. The rates of reaction in carbon tetrachloride and in chloroform, in both of which solvents all the evidence points to the iodine existing as simple molecules, are identical, whereas the viscosities of the two solvents are widely different. As shown above, the state of iodine in benzene and diamyl ether is complex and so prevents a consideration of the rates carried out in them with respect to the above; but the evidence from solutions in chloroform and in carbon tetrachloride alone suggests that the organic solvents do not themselves diffuse through the cuprous iodide film.

Adopting this theory, we have still to consider the mechanism by which the iodine molecules diffuse through the film. Three mechanisms appear to be possible: (1) The iodine might diffuse through large cracks in the film (a type of gaseous diffusion); (2) it might diffuse through small pores in the film, possibly in loose union with the cuprous iodide; (3) the diffusions might take place through atomic holes in the cuprous iodide crystal lattice.

The diffusion mechanism of (1) would depend on the vapour pressure of the iodine, which would increase rapidly with rise of temperature, and this would result in a relatively large temperature coefficient. The very small temperature coefficient observed is evidence against this. Mechanism (2), passage of iodine through pores little larger than the molecules themselves, is not impossible. If some type of attraction exists between the iodine and the cuprous iodide little energy would be required for the diffusion. The small temperature coefficient found is some evidence for this. (3) According to the theories developed by Jost and Schottburg "atomic holes" exist as lattice defects in any crystalline material, and it is possible that diffusion of iodine may take place in this manner. This theory of diffusion has, of course, attracted much attention during recent years. Like mechanism (2), this process would require little energy, and it is not possible to distinguish between (2) and (3) by a consideration of the temperature coefficient.

The authors thank the Chemical Society for a grant, and one of them (M. H. E.) is indebted to the Governing Body of University College, Exeter, for a grant from the Andrew Simons Fund.

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[Received, September 7th, 1946.]

212. Deoxypentose Nucleic Acids. Part I. Preparation of the Tetrasodium Salt of the Deoxypentose Nucleic Acid of Calf Thymus.

By J. MASSON GULLAND, D. O. JORDAN, and C. J. THRELFALL.

The preparation of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus is described by a method in which the nucleoprotein is first isolated and then decomposed; during these processes the reaction did not vary significantly from pH 7. The analytical data support the relative proportions of nucleotides indicated by titration (Gulland, Jordan, and Taylor, Part II, this vol., p. 1131).

GULLAND, BARKER, and JORDAN (*Ann. Rev. Biochem.*, 1945, **14**, 175) have suggested that the direct isolation of nucleic acids from tissues may lead to a degraded product, and they consider that a more satisfactory procedure is to isolate and subsequently decompose the nucleoprotein. In the method which has been developed, therefore, the deoxypentose nucleoprotein of calf thymus was first isolated by making use of the remarkable difference in solubility of the nucleoprotein in sodium chloride solutions of different strengths described by Mirsky and Pollister (*Proc. Nat. Acad. Sci. U.S.*, 1942, **28**, 344; *Biol. Symposia*, 1943, **10**, 24). The deoxypentose nucleic acid was then separated from the protein by the method introduced by Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425).

The material obtained by this preparation gave satisfactory analytical figures for carbon, hydrogen, phosphorus, and sodium, but the nitrogen value was low, being 15.4% compared with the theoretical value of 15.9% based on a polynucleotide containing the four nucleotides in equimolecular quantities. Furthermore the ratio of the purine nitrogen content to that of pyrimidine nitrogen was low, a mean value of 1.6 being obtained in place of the theoretical value of 2.0. These data may be interpreted with the aid of the results of electrometric titration (Part II, *loc. cit.*), which, whilst indicating that for every four atoms of phosphorus there is 1.0 radical of thymine and 1.0 of guanine, suggest that the amount of cytosine may be as high as 1.2 radicals and of adenine as low as 0.8 radical. Re-calculation of the theoretical nitrogen analysis on this basis gives a value of 15.5%, and the purine nitrogen/pyrimidine nitrogen ratio has the value 1.6. These data are in satisfactory agreement with the observed results. The theoretical values for carbon, hydrogen, phosphorus, and sodium are not affected appreciably by this change in the nucleotide ratio in the statistical polynucleotide.

EXPERIMENTAL

Isolation of the Tetrasodium Salt of the Deoxypentose Nucleic Acid of Thymus Gland.—Fresh frozen calf thymus glands (54.5 kg.) were minced and suspended in 0.9% sodium chloride (54 l.) and milled to produce a fine suspension. This suspension was centrifuged (6300 r.p.m.) and the solid material resuspended in 0.9% sodium chloride (45.5 l.) and milled and centrifuged as before. The ribonucleoproteins, together with cytoplasmic material, were obtained from the combined extracts (120 l.) by adding an equal volume of industrial methylated spirit, and the precipitated solid was washed by decantation with 50%, then 100% industrial methylated spirit, collected, and dried in a vacuum at room temperature. Yield, 2.68 kg.

The tissues, which were now free of material containing pentose, were suspended in 10% sodium chloride (214 l.) with vigorous mechanical stirring at 0°. At this stage the viscosity of the solution increased considerably (cf. Mirsky and Pollister, *loc. cit.*). After extraction at 0° for 48 hours, the insoluble material was removed by centrifuging (6300 r.p.m.) and the deoxypentose nucleoprotein precipitated from the resultant solution (pH 6.5) by the addition of an equal volume of industrial methylated spirit. The precipitated solid was washed with 70%, then 100% industrial methylated spirit and dried in a vacuum at room temperature. Yield, 1.69 kg. of a very slightly yellow fibrous solid.

The nucleoprotein (500 g.) was powdered to assist solution and dissolved in 10% sodium chloride (45.5 l.) with vigorous mechanical stirring. The solution, which was viscous, was clarified by centrifuging (6300 r.p.m.). To the clear solution was added an equal volume of a mixture of chloroform (35 parts) and amyl alcohol (10 parts), and the mixture was emulsified by rapid mechanical stirring. The emulsion was then separated by centrifuging (DeLaval, model "500", disc type bowl, 5500 r.p.m.) into three parts: (i) the chloroform-amyl alcohol mixture, (ii) a solution containing the sodium salt of deoxypentose nucleic acid and nucleoprotein, (iii) a gel of protein hydrochloride and the chloroform-amyl alcohol mixture. The protein gel remained in the bowl of the centrifuge whereas the chloroform-amyl alcohol mixture and the solution of nucleic acid and nucleoprotein were discharged from separate outlets. The last mentioned solution was again emulsified with the chloroform-amyl alcohol mixture and the process repeated until no gel was formed on emulsification; this required nine emulsifications. The sodium salt of the deoxypentose nucleic acid was precipitated by the addition of an equal volume of industrial methylated spirit, washed free from chloride with 70% industrial methylated spirit, then 100% ethyl alcohol, and finally ether, and dried in a vacuum at room temperature. Yields from two 500 g. quantities of nucleoprotein were 130 g. and 150 g. of a white fibrous solid giving negative biuret and Sakaguchi tests [Found on sample dried at 110° in a vacuum over phosphoric oxide: C, 35.5, 35.5,

35.3; H, 3.68, 3.83, 3.56; N, 15.3, 15.3, 15.4; P, 9.35, 9.32, 9.32; Na, 6.9, 6.8 (gravimetric), 7.1 (colorimetric). Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine, adenine, cytosine, and thymine deoxypentose nucleotides, *i.e.* $(C_{26}H_{48}O_{24}N_{15}P_4Na_4)_x$: C, 35.4; H, 3.4; N, 15.9; P, 9.4; Na, 6.95. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine and thymine, and 1.2 mols. of cytosine and 0.8 mol. of adenine deoxypentose nucleotides, *i.e.* $(C_{26.8}H_{48.8}O_{24.2}N_{14.6}P_4Na_4)_x$: C, 35.4; H, 3.4; N, 15.5; P, 9.4; Na, 6.98%. In both cases the additional HONa atoms of the two terminal nucleotides of a straight-chain polynucleotide have been ignored, since their contribution is negligible if the size of the polynucleotide is large].

Determination of Purine Nitrogen/Pyrimidine Nitrogen Ratio.—The method used was that of precipitation of purines with silver sulphate (Schmidt and Levene, *J. Biol. Chem.*, 1938, **126**, 423). The sodium salt of deoxypentose nucleic acid (*ca.* 30 mg.) was hydrolysed by boiling under reflux with 5% sulphuric acid (7 ml.) for 1 hour. When cold, the solution was diluted to 25 ml., the total nitrogen was determined on a portion (2 ml.), and 2 ml. samples were treated with an equal volume of saturated silver sulphate. The solution containing the precipitate of the silver salts of guanine and adenine was cooled at 0° for $\frac{1}{2}$ hour. The precipitate was separated by centrifuging and washed twice by stirring at 0° with a saturated solution of silver sulphate (2 ml.) followed by centrifuging. The solution was combined with the washings and analysed for pyrimidine nitrogen. The precipitate was decomposed with dilute hydrochloric acid (2 ml.), and the silver chloride removed by centrifuging and washed twice with dilute hydrochloric acid (2 ml.). The solution was combined with the washings and analysed for purine nitrogen. The purine nitrogen/pyrimidine nitrogen ratio was found to be 1.60, 1.63, 1.60, 1.58, 1.57 for five separate hydrolyses; mean, 1.60. The discrepancy between this value and the theoretical of 2 for a statistical polytetranucleotide is greater than the experimental error indicated by the Table. Nevertheless we should not have inclined to attribute undue significance to the ratio, were it not for the agreement between it, the analytical data, and the results of electrometric titration; this uniformity of trend does suggest that the purine/pyrimidine nitrogen now recorded has real meaning.

In order to confirm the accuracy of the method claimed by Schmidt and Levene (*loc. cit.*), a series of analyses of known purine and pyrimidine derivatives was performed; representative results are recorded in the Table. Determination of the purine/pyrimidine nitrogen ratio of two samples of yeast ribonucleic acid was made for comparison, the results being 1.84, 1.86; 1.84, 1.90.

Substance.	Total N, mg.	Purine N, mg.	Pyrimidine N, mg.	Recovery, %.
Guanine	10.42, 10.17, 10.38, 9.80	10.48, 10.29, 10.56, 9.70	—	100.6, 101.2, 101.7, 99.0
Adenine	10.50	10.22	—	97.3
Hypoxanthine.....	8.06	7.90	—	98.1
Guanosine	9.53, 8.78	9.62, 8.91	—	101.0, 101.4
Adenosine	8.49, 9.40	8.43, 9.30	—	99.3, 98.9
Thymine	1.46, 7.20	—	1.39, 7.40	94.3, 102.8
Cytidine	6.45	—	6.44	99.9
Uridine.....	2.98	—	2.99	100.3
Guanine * }	9.40	9.30	—	98.0
Uracil * }	6.95	—	7.15	102.9

* Mixed.

Analytical Methods.—The sodium salt of deoxypentose nucleic acid is extremely hygroscopic when dried, as in this instance, at 110°/0.1 mm. over phosphoric oxide, and special technique was required in order to minimise exposure of the dried material to atmospheric moisture. Estimations of carbon by combustion presented some difficulty owing to the occlusion of carbon by the sodium metaphosphate residue in the boat, but this problem was solved by the addition of small quantities of anhydrous potassium chlorate to the fused mass at the end of the combustion. Determinations of nitrogen were made by a modified micro-Kjeldahl technique embodying the methods of Elek and Sobotka (*J. Amer. Chem. Soc.*, 1926, **48**, 501) and Friedrich ("Die Praxis der quantitativen organischen Mikroanalyse," 1933, Deuticke, Leipzig and Vienna); of phosphorus by a modification of the method of Embden (*Z. physiol. Chem.*, 1920, **113**, 138); and of sodium either gravimetrically (as sodium sulphate after removal of phosphate as barium phosphate) or colorimetrically (Hoffman and Osgood, *J. Biol. Chem.*, 1938, **124**, 347).

It is a pleasure to acknowledge our gratitude to Boots Pure Drug Company Ltd. for carrying out the large scale operations; to the British Empire Cancer Campaign for a grant which defrayed part of the cost; and to Imperial Chemical Industries Ltd. for the loan of apparatus. We wish also to record our thanks to Mr. J. E. Still, B.Sc., for the analyses for C, H, N, and P, and to Mr. H. F. W. Taylor, B.Sc., and Mr. J. M. Creeth, B.Sc., for the sodium analyses.

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[Received, November 2nd, 1946.]

213. Deoxypentose Nucleic Acids. Part II. Electrometric Titration of the Acidic and the Basic Groups of the Deoxypentose Nucleic Acid of Calf Thymus.

By J. MASSON GULLAND, D. O. JORDAN, and H. F. W. TAYLOR.

The acidic and the basic groups of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus and of barium thymate derived therefrom have been titrated electrometrically, employing hydrogen and glass electrodes. This polynucleotide is found to possess three amino-, two purine-pyrimidine enolic hydroxyl, four primary phosphoryl, and not more, and probably less, than 0.25 secondary phosphoryl dissociations for every four atoms of phosphorus. These data are consistent with a chain structure for this acid in which branching, if it occurs, is infrequent as compared with yeast ribonucleic acid. The main internucleotide bond is an ester linkage. For every four atoms of phosphorus it is found that there are 1.0 guanine, 1.0 thymine, 1.0 to 1.2 cytosine, and 1.0 to 0.8 adenine radicals.

The initial dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus obtained by titrating from pH 6.9 with acid and alkali are abnormal, being displaced from the back-titration curves. This discrepancy between the forward- and back-titration curves persists in high concentrations of neutral salt. It is concluded that the purine-pyrimidine hydroxyl groups and some of the amino-groups are blocked, most probably by a hydrogen bond between these groups. The significance of this linkage in the macromolecular structure of the tetrasodium salt of the deoxypentose nucleic acid is discussed.

THE conflicting results obtained previously from investigations of the acid-base properties of thymus deoxypentose nucleic acid (Steudel, *Z. physiol. Chem.*, 1912, **77**, 497; Feulgen, *ibid.*, 1919, **104**, 189; Levene and Simms, *J. Biol. Chem.*, 1925, **65**, 519; 1926, **70**, 327; Makino, *Z. physiol. Chem.*, 1935, **232**, 229; 1935, **236**, 201; Bredereck, Köthnig, and Lehmann, *Ber.*, 1938, **71**, 2613; Bredereck and Köthnig, *ibid.*, 1939, **72**, 121; Ahlström, Euler, Fischer, Hahn, and Högberg, *Arkiv Kemi, Min. Geol.*, 1945, **20**, A, 1) may be ascribed to the different degrees of degradation of the samples studied (Schmidt, Pickels, and Levene, *J. Biol. Chem.*, 1939, **127**, 251; Cohen, *ibid.*, 1942, **146**, 471; Tennent and Vilbrandt, *J. Amer. Chem. Soc.*, 1943, **65**, 424; Gulland, Barker, and Jordan, *Ann. Rev. Biochem.*, 1945, **17**, 175). In all probability the least degraded specimens which have hitherto been examined were those prepared by the method of Bang (Hofmeister's "Beiträge chem. Physiol. Path.", 1903, **4**, 331) and studied conductimetrically by Hammarsten (*Biochem. Z.*, 1924, **144**, 383) and electrometrically by Jorpes (*Biochem. J.*, 1934, **28**, 2102) and Stenhagen and Teorell (*Trans. Faraday Soc.*, 1939, **35**, 743). They were found to possess four acid-dissociating groups per hypothetical tetranucleotide, having the very approximate pK_a' values of 2.4, 3.7, 4.3, and 5.2. The Hammarsten-Bang method of isolation, however, gave a product which on analysis was found to be very deficient in nitrogen and phosphorus (N, 11.97; P, 7.09%; Hammarsten, *loc. cit.*) when compared with the theoretical for the tetrasodium salt (N, 15.85; P, 9.37%). Furthermore, Hammarsten studied the free acid obtained from the sodium salt by the action of hydrochloric acid; as will be shown in this paper this treatment causes an irreversible change in that the free acid isolated from solutions more acid than pH 3.5 does not show the same acid-base properties as the sodium salt isolated at pH 7.0.

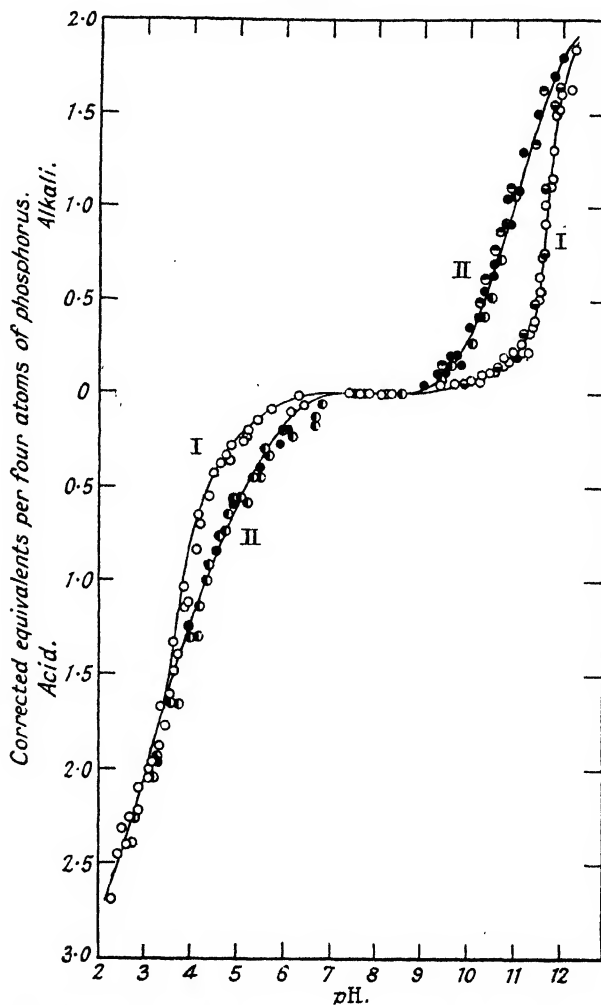
The sodium salt of calf thymus deoxypentose nucleic acid which has been studied in this investigation was isolated by a mild method (Gulland, Jordan, and Threlfall, Part I, this vol., p. 1129), throughout which the solution employed did not vary significantly from pH 7.0.* The solid was fibrous and dissolved in water to give a faintly opalescent solution, having a pH of 6.90, which exhibited marked structural viscosity and streaming birefringence (Creeth, Gulland, and Jordan, Part III, this vol., p. 1141). A second specimen, prepared by the Hammarsten-Bang procedure and supplied by Professor Caspersson through Professor Astbury in 1939, has also been studied. It was found to contain a small amount of protein which was removed by the method of Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425), and is believed to be identical with that studied with ultracentrifuge and viscosity methods by Signer, Caspersson, and Hammarsten (*Nature*, 1938, **141**, 122) and with X-ray methods by Astbury and Bell (*ibid.*, p. 747).

* It is necessary to correct a point in the paper of Tennent and Vilbrandt (*J. Amer. Chem. Soc.*, 1943, **65**, 424). The sample of "Thymonucleic acid TNA2, prepared by Gulland", referred to by these authors, was a purchased commercial sample, and the "barium thymate BT1, prepared by Gulland" was made from it by the usual method. These were given to Professor Astbury in 1939 with a warning that their purity and homogeneity was open to doubt; they were not intended for the type of investigation to which they have been put by Tennent and Vilbrandt, and in our view results obtained with them are of no value in connection with nucleic acid structure.

Results of the Present Investigation.—All electrometric titration curves have been corrected at the extremes of pH for the titration of the water by the method of Jordan and Taylor (*J.*, 1946, 994).

(i) *Titration of the sodium salt of thymus deoxypentose nucleic acid.* The titration curve of this sample is shown in Fig. 1, curve I. It will be seen that on the addition of acid or alkali to

FIG. 1.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus :

I. *Titration with acid or alkali from pH 6.9, ○, ●. The smooth curve drawn through these points is calculated for 1 equiv. each of pK'_a values 2.6, 3.5, 5.2, 10.4 and 11.4.*

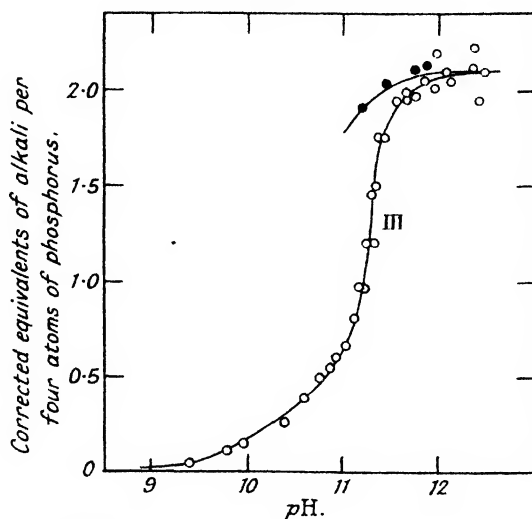
II. *Back titration with acid from pH 12.0, ●, ● and with alkali from pH 2.5, ○, ○.*

Points marked ● and ● obtained with "Alki" glass electrode (Cambridge Instrument Co., Ltd.); all other points obtained with hydrogen electrode.

the solution in water no groups are titrated at first between pH 5.0 and 11.0, but that outside these limits there occurs a rapid liberation of groups titrating in the ranges pH 2.0 to 6.0 and pH 9.0 to 12.0. On back titration either with acid from pH 12.0 or with alkali from pH 2.5, a curve (II) is obtained which is different from that representing the initial titration, and it is significant that the same curve (II) is obtained whether the back titration is with alkali from pH 2.5 or with acid from pH 12.0. This complete identity of the back-titration curves suggests that acid and alkali have an identical effect in liberating both sets of groups.

The back-titration curve exhibits a well-defined point of inflection in the neutral region, and shows incipient points of inflection in the regions of pH 12.0 and pH 2.0, corresponding respectively to approximately 2.0 equivalents of alkali and 3.0 equivalents of acid for each four atoms of phosphorus. There is some difficulty in interpreting electrometric titration

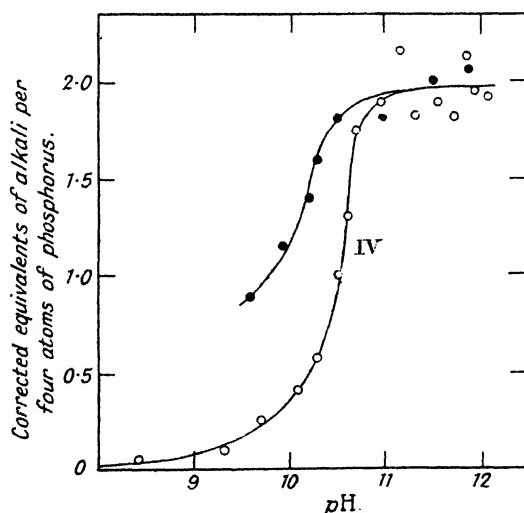
FIG. 2.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus in M-potassium chloride.

Titration with alkali from pH 6.9, ○ ; back titration with acid from pH 12.5, ●.

FIG. 3.



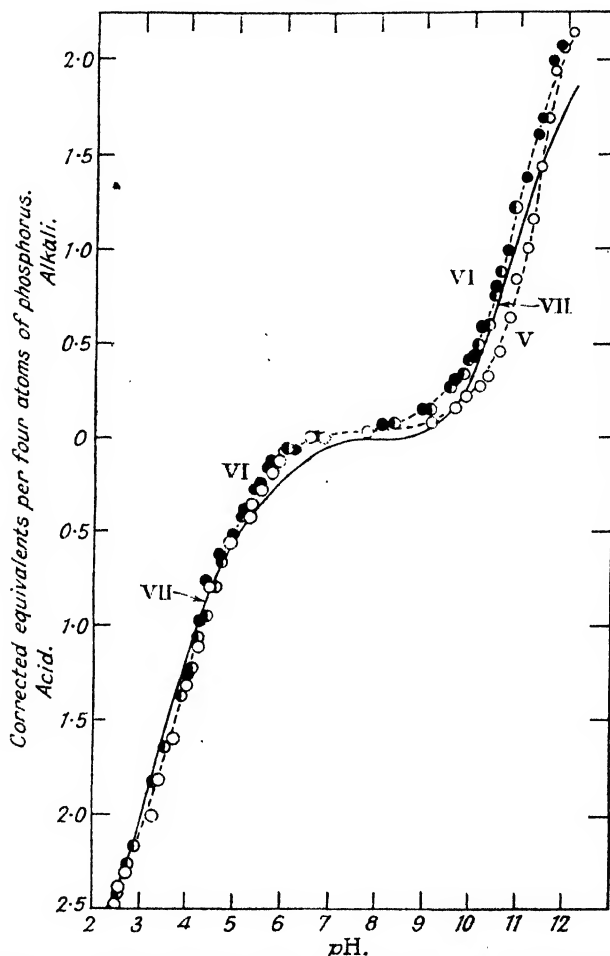
The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus in 2.5M-guanidine sulphate.

Titration with alkali from pH 6.9, ○ ; back titration with acid from pH 12.0, ●.

data above pH 11.0 and below pH 3.0 owing to the dependence of the water correction on the ionic strength (Jordan and Taylor, *loc. cit.*), which, for a polybasic substance such as nucleic acid, cannot be estimated with certainty. In obtaining the data given in Fig. 1, the assumption has been made that the acidic and basic groups contribute independently to the ionic strength. This approximation is justified by the fact that no appreciable proportion of the phosphorus

atoms carry more than one dissociating group (see below). It appeared desirable, however, to have additional confirmation of the number of groups titrating in the alkaline region, and titration of the sodium salt of thymus deoxypentose nucleic acid was therefore carried out in *m*-potassium chloride. The presence of the potassium chloride has the effect of masking all other contributions to the ionic strength (Cohn, Green, and Blanchard, *J. Amer. Chem. Soc.*, 1937, 59, 509), and the water correction is obtained from a titration of *m*-potassium chloride. The results of this titration, which are given in Fig. 2, curve III, show conclusively that the

FIG. 4.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus after alkaline treatment followed by precipitation with alcohol at pH 7 :

V. Titration with alkali from pH 6.7, ○.

VI. Titration with acid from pH 6.7, ○ ; back titration with alkali from pH 2.5, ● ; back titration from pH 12.0, ●.

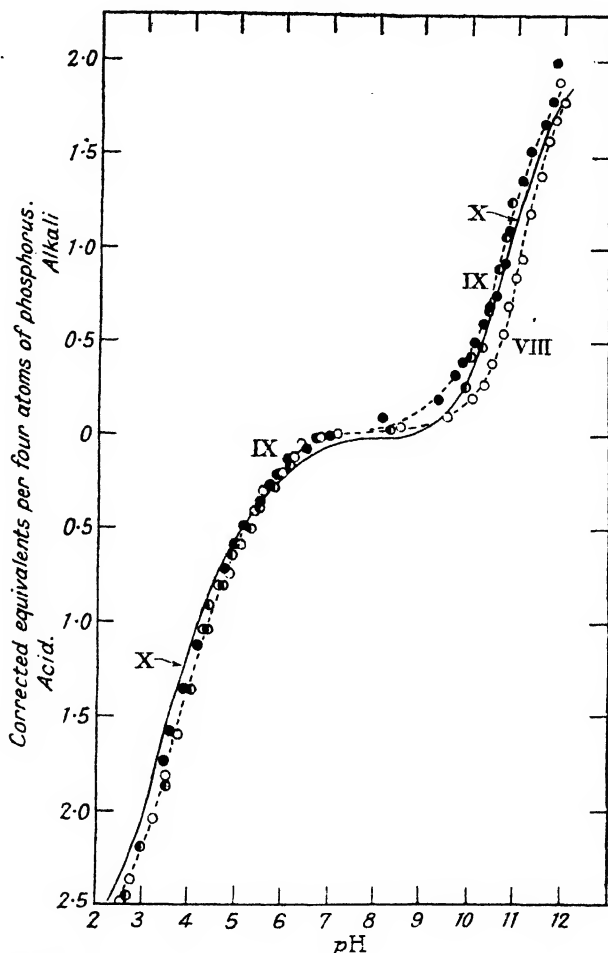
VII (full curve). Mean titration curve of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus from Fig. 1.

number of groups dissociating in the range pH 8.0 to 12.0 is 2.05. Owing to the ease with which precipitation of the deoxypentose nucleic acid occurs in the presence of *m*-potassium chloride when acid is added, a complete back titration below pH 11.2 was not practicable; the data which have been obtained, however, are sufficient to indicate that the discrepancy between the forward- and back-titration curves described above persists in the presence of *m*-potassium chloride. Very similar results were obtained by titration in 2.53*M*-guanidine sulphate ($[\text{C}(\text{NH}_2)_3]_2\text{SO}_4$; Fig. 3, curve IV). Owing, however, to the existence of an unsteady liquid-

junction potential between this solution and the saturated potassium chloride bridge, the pH values were not very reproducible, especially in strongly alkaline solutions.

(ii) *Titration of the sodium salt of thymus deoxypentose nucleic acid precipitated with alcohol at pH 7.0 after treatment with alkali at pH 12.0, or with acid at pH 3.0.* The titration curves of an alkali-treated sample are shown in Fig. 4, curves V and VI; similar results were obtained with two other samples. The results of titration on the alkaline side of neutrality resemble those obtained with the original substance, in that a shift in the dissociation curve is observed

FIG. 5.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus after acid treatment followed by precipitation with alcohol at pH 7:

VIII. Titration with alkali from pH 7.1, ○.

IX. Titration with acid from pH 7.1, ○; back titration from pH 2.3, ●; back titration from pH 12.0, ●.

X (full curve). Mean titration curve of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus from Fig. 1.

on back titration, although to a somewhat smaller extent. No such effect, on the other hand, was observed on the acid side. The back-titration curves from pH 12.0 or pH 2.5 are identical, and are very similar to the curve obtained with the original substance.

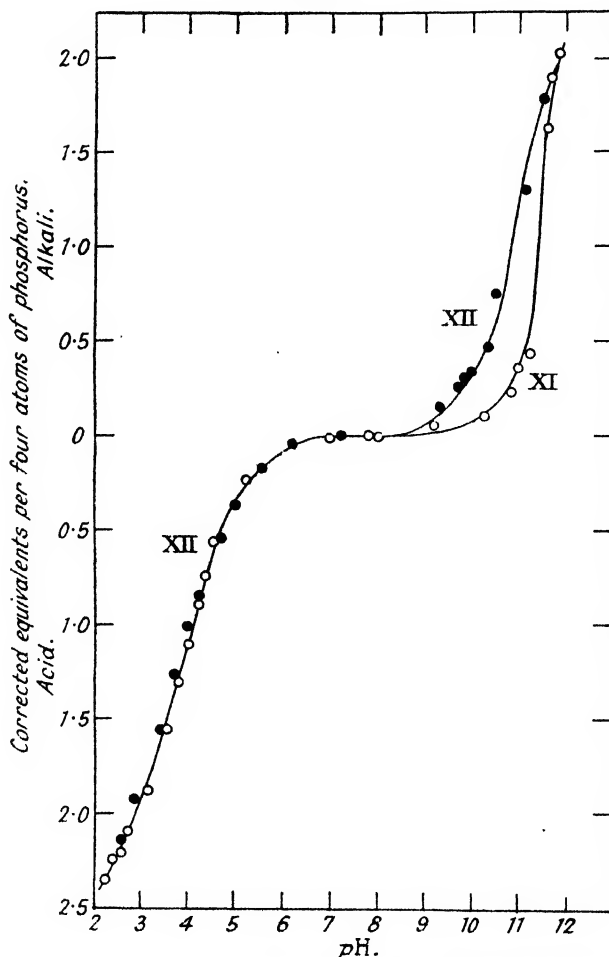
The results obtained with an acid-treated specimen (Fig. 5, curves VIII and IX) are almost identical with those described above for the alkali-treated material.

(iii) *Titration of the sodium salt of thymus deoxypentose nucleic acid supplied by Professor Caspersson.* The titration curves of this sample are shown in Fig. 6, curves XI and XII, and

are intermediate between those of the alkali- and acid-treated materials prepared by us and those of our original material. Viscosity studies (Creeth, Gulland, and Jordan, *loc. cit.*) support the view that, compared with the acid prepared by us, the sample of Caspersson exhibits different, probably less, hydrogen bonding (see below) and lower viscosity.

(iv) *Titration of the barium salt of thymic acid.* On treating thymus deoxypentose nucleic acid with dilute sulphuric acid at 80°, quantitative removal of guanine and adenine takes place (Feulgen, *Z. physiol. Chem.*, 1918, 101, 296; Feulgen and Landmann, *ibid.*, 102, 262; Brederick

FIG. 6.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus supplied by Professor Caspersson :

XI. Titration with alkali from pH 7.8, ○.

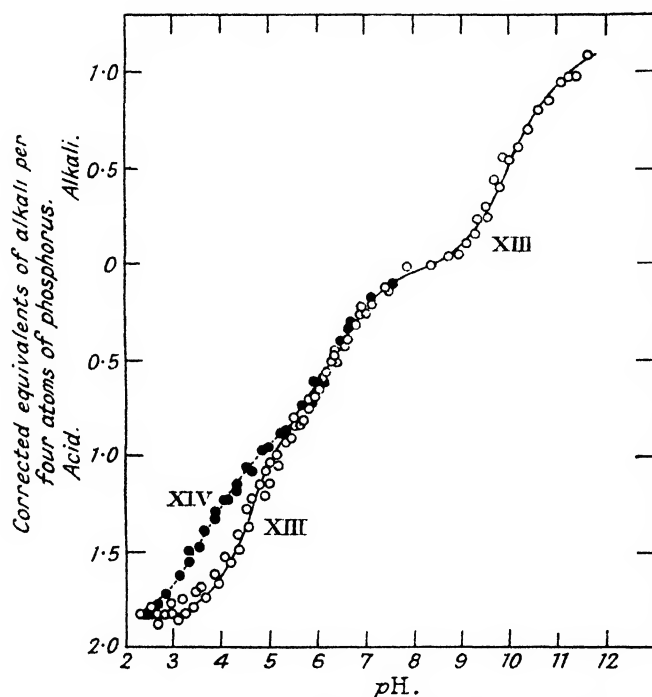
XII. Titration with acid from pH 7.8, ●; back titration from pH 11.8, ○.

and Müller, *Ber.*, 1939, 72, 115); the resulting thymic acid is isolated as its barium salt. The empirical formula weight of this substance is defined, for convenience, as the amount containing 4 g.-atoms of phosphorus, and the values obtained from the phosphorus contents of the two preparations studied were 1310 and 1315. The electrometric titration curve calculated on the basis of these formula weights is shown in Fig. 7, curve XIII, well-marked points of inflection being observed at pH 2.5, 8.0 and 11.5 after the neutralisation of 1.85 and 1.0 equivalents respectively. A titration has also been carried out in the presence of formaldehyde in order to ascertain what proportion of the more acidic dissociation represents that of an amino-group (curve XIV).

Discussion.—(i) *The nature of the acidic and the basic groups of deoxypentose nucleic acid.* The problem of the initial structure of deoxypentose nucleic acid before alkali or acid treatment will be considered in section (ii) of this discussion, and in this section the back-titration curve (Fig. 1, curve II) only will be treated.

Owing to the fact that the deoxyribonucleotides have not yet been isolated in quantities sufficient to permit an investigation by electrometric methods, it is necessary to refer to dissociation-constant data of the ribonucleotides in order to interpret this curve. This procedure is to some extent justified by the fact that the pK_a' values of the amino-groups of adenylic

FIG. 7.



The dissociation curves of the barium salt of thymic acid :

XIII. Titrations with acid and alkali from approximately pH 7, O. The smooth curve drawn through these points is calculated for 1.1 equivs. of $pK_a' 4.6$, 0.75 equiv. of $pK_a' 6.5$, and 1.0 equiv. of $pK_a' 10.0$.

XIV. Titration in 1.875% formaldehyde solution, ●.

(The zero of equivalents is fixed arbitrarily at pH 8.4, the titrations being carried out on two samples of slightly different barium content.)

and cytidylic acids do not differ very greatly from those of adenine and cytosine respectively, as shown by the following data :

Adenine	4.15	Adenylic acid.....	3.70 ¹
Cytosine	4.60 ¹	Cytidylic acid	4.24 ¹

¹ Data of Levene and Simms (*loc. cit.*).

It is not expected, therefore, that replacement of *d*-ribose by deoxypentose would give rise to any considerable change in the pK_a' values.

There has been some confusion in the literature between the pK_a' values assigned to the amino- and the primary phosphoryl dissociations of nucleic acids. Levene and Simms (*loc. cit.*) considered the groups dissociating in the range pH 2.0 to 6.0 to be the amino-groups, whereas Hammarsten (*loc. cit.*) and Fletcher, Gulland, and Jordan (*J.*, 1944, 33) considered them to be the primary phosphoryl dissociations. Consideration of the pK_a' values for the

nucleosides and sugar phosphates (given below) in the light of the modern theory of zwitterions points conclusively to the former view being correct.*

Adenosine	3.45	(Levene and Simms, <i>loc. cit.</i>).
Sugar phosphates...	pK_a' , 0.8 to 1.1; pK_a' , 6.0 to 6.5	(Kumler and Eiler, <i>J. Amer. Chem. Soc.</i> , 1943, 65 , 2355).
Adenylic acid	pK_a' , 0.89; pK_a' , 3.70; pK_a' , 6.01	(Levene and Simms, <i>loc. cit.</i>).

The pK_a' value of adenylic acid is clearly that of a primary phosphoryl dissociation, the pK_a' an amino-dissociation, and the pK_a' a secondary phosphoryl dissociation. At the isoelectric point, therefore, nucleic acids will exist almost entirely in the zwitterionic form.

The dissociations which will be titrated in the range pH 2.5 to 8.0 are therefore those of the amino- and the secondary phosphoryl groups. Examination of the lower portion of the back-titration curve (Fig. 1, curve II) shows that groups of both types are present, although the amount of secondary phosphoryl dissociation for every four atoms of phosphorus is relatively very small (see below). The curve is in approximate agreement with a theoretical curve constructed for 1.0 equivalent each, for every four atoms of phosphorus, of the amino-dissociations of guanylic, adenylic, and cytidylic acids, the pK_a' values of which are 2.3, 3.7, and 4.24 respectively (Levene and Simms, *loc. cit.*; Fletcher, Gulland, and Jordan, *loc. cit.*). It appears, however, that the pK_a' value of the amino-group of cytidylic acid (*viz.*, 4.24) which has been assumed for the amino-group of cytosine deoxypentose nucleotide is low, and much better agreement with the experimental curve is obtained by employing the pK_a' values of 2.5, 3.5, and 5.2 for constructing the theoretical curve; the curve shown in Fig. 1 is calculated on this basis.

The titration curve in the range pH 5.5 to 7.5 indicates the presence of a small amount of a group having a pK_a' value of 6.0 to 6.5, which is considered to be a secondary phosphoryl group. The determination of the exact quantity of this dissociation is dependent upon a precise knowledge of its pK_a' value and of the amounts of the amino-dissociations and their pK_a' values, but using 6.5 for the pK_a' value of the secondary phosphoryl dissociation, which is that observed for thymic acid, and assuming that there is no overlap of the amino- and the secondary phosphoryl dissociations above pH 6.5 (*i.e.*, no amino-dissociation greater than pK_a' 4.5), the amount of secondary phosphoryl dissociation is 0.25 equivalent for every four atoms of phosphorus. This represents the maximum amount of this group which can be present. Since, however, the pK_a' value of the weakest amino-group is of the order of 5.2, overlapping of the dissociations above pH 6.5 must occur, and thus the amount of the secondary phosphoryl dissociation present will be less than the maximum value.

The analysis of the sodium salt of deoxypentose nucleic acid shows that there are four sodium atoms for every four atoms of phosphorus, and in view of the fact that the amount of secondary phosphoryl dissociation is small, the four atoms of sodium must be combined largely or entirely with four primary phosphoryl dissociations. The deoxypentose nucleic acid of calf thymus differs in this respect markedly from the ribonucleic acids of yeast (Fletcher, Gulland, and Jordan, *loc. cit.*) and of *Calliphora erythrocephala* (Khouvine and Grégoire, *Bull. Soc. Chim. biol.*, 1944, **16**, 421), both of which show 1.0 equivalent of secondary phosphoryl dissociation (on correction for the phosphorus analysis) for every four atoms of phosphorus, and it cannot therefore possess the branched chain structure postulated for yeast ribonucleic acid by Fletcher, Gulland, and Jordan (*loc. cit.*). The data recorded are, however, consistent with the view that the thymus deoxypentose nucleic acid of calf thymus has a long, unbranched chain structure (Signer, Caspersson, and Hammersten, *loc. cit.*; Astbury and Bell, *loc. cit.*).

The groups titrating in the range pH 8.0 to 12.0 are considered to be the purine-pyrimidine hydroxyl groups of thymine and guanine deoxypentosides, and the upper part of the back-titration curve is in agreement with a theoretical curve constructed for 1.0 equivalent each of pK_a' values 10.4 and 11.4. The corresponding pK_a' value for thymine is 9.94 (Levene, Bass, and Simms, *J. Biol. Chem.*, 1926, **70**, 229; and confirmed by us) and for guanylic acid, 9.36 (Levene and Simms, *loc. cit.*), which, although of the same order of magnitude as the upper dissociations of deoxypentose nucleic acid, are nevertheless appreciably lower. The same effect is seen to a lesser extent in yeast ribonucleic acid which shows 2.0 dissociations of pK_a' 10.2 as compared with 9.36 for guanylic acid and 9.43 for uridylic acid (Levene and Simms, *loc. cit.*; Fletcher, Gulland, and Jordan, *loc. cit.*). The reason for this discrepancy is not clear,

* Acceptance of this view does not alter the main conclusions of Fletcher, Gulland, and Jordan about the structure of yeast ribonucleic acid, except that the triply-bound phosphoryl group is not necessarily that of uridylic acid.

especially in view of the better agreement which exists between the pK'_a values for the amino-dissociations of the ribonucleotides and of a yeast ribonucleic acid. It may, however, be related to the degree of polymerisation of the nucleic acid since it is not observed in thymic acid, which is considered to have a low molecular weight (see below).

The data given in Fig. 2, curve III, show that, other than the purine-pyrimidine hydroxyl groups, there are no dissociating groups titrating with alkali which have a pK'_a value in water less than at least 13.5. This confirms the absence of free sugar hydroxyl groups in this sample, since the pK'_a values of the primary hydroxyl dissociations of many sugars are in the region of 12.5 (Hirsch and Schlags, *Z. physikal. Chem.*, 1929, **141**, A, 387; Stearn, *J. Physical Chem.*, 1931, **35**, 2226; Urban and Shaffer, *J. Biol. Chem.*, 1932, **94**, 697; Urban and Williams, *ibid.*, 1933, **100**, 237), and suggests that no other sugar than a deoxypentose is present in any appreciable quantity in this sample of deoxypentose nucleic acid of thymus. Furthermore, taken in conjunction with the presence of one primary phosphoryl dissociation for every atom of phosphorus, the guanine, adenine, and cytosine dissociations and the guanine and thymine hydroxyl dissociations, this fact supports the view that the internucleotide bond is an ester linkage between the phosphoryl groups and the two hydroxyl groups of the sugar which are not involved in the glycosidic ring structure. Other types of linking may, however, exist in the nucleic acid, but the sensitivity of the titration method precludes the occurrence of such other linkages to a greater extent than one for every ten to twenty nucleotides.

The titration of thymic acid, taken in conjunction with the preceding data for deoxypentose nucleic acid, supplies information concerning the proportions of the four bases guanine, adenine, cytosine, and thymine present in this sample of nucleic acid. The titration curve for thymic acid (Fig. 7) shows 1.0 dissociation per four atoms of phosphorus in the pH range 8.0 to 12.0; this group can only be the enolic hydroxyl group of thymine. The 2.0 dissociations therefore observed in this pH range for deoxypentose nucleic acid (see above) must indicate the presence of one molecule each of thymine and guanine for every four atoms of phosphorus. It is not possible to determine with certainty the relative proportions of cytosine and adenine from the titration data of the sodium salt of deoxypentose nucleic acid, although the total amount of these groups is approximately 2.0. Thymic acid, however, possesses for every four atoms of phosphorus 1.0 to 1.2 dissociations of pK'_a 4.5 which must be the amino-dissociation of cytosine, and thus it is probable that the ratio of cytosine to adenine in the deoxypentose nucleic acid is as 1.0—1.2 is to 1.0—0.8.

The presence in barium thymate of 0.75 equivalent of a secondary phosphoryl dissociation for every four atoms of phosphorus suggests, on the basis of the straight-chain structure for deoxypentose nucleic acid, that the average number of nucleotides per molecule of thymic acid is approximately 5, and thus that the average molecular weight of the free acid is of the order of 1200.

(ii) *The macromolecular structure of deoxypentose nucleic acid.* As is shown in Fig. 1, the amino- and the enolic hydroxyl groups of thymus deoxypentose nucleic acid are partly or completely blocked until the material has been treated with acid or alkali; an irreversible change then takes place with the accompanying liberation of titratable groups. The release of the groups on treatment with alkali takes place sharply in the neighbourhood of pH 11.5, but less sharply in the range pH 3.5 to 4.5 on treatment with acid. In both cases equilibrium is established almost instantaneously, and the liberation of groups is accompanied by a marked fall in the viscosity and a disappearance of streaming birefringence (Hammarsten, *loc. cit.*; Vilbrandt and Tennent, *J. Amer. Chem. Soc.*, 1943, **65**, 1806; Creeth, Gulland, and Jordan, *loc. cit.*).

The decrease in viscosity brought about by the addition of acid or alkali was considered by Vilbrandt and Tennent (*loc. cit.*) to be caused by a depolymerisation which was slowly reversed when the solution was returned to neutrality. Our results show that such a depolymerisation cannot involve the rupture of the internucleotide ester linkages since no increase of secondary phosphoryl dissociation is observed in the back-titration curve. The complete identity of the back-titration curves from pH 2.5 and pH 12.0 strongly suggests that acid and alkali have the same effect in liberating the amino- and the hydroxyl groups. Two possibilities may be considered to explain this behaviour. It could be caused by easily hydrolysed radicals, hitherto unidentified in the breakdown products of the nucleic acid, which either substitute in the amino- and the hydroxyl groups separately or form a bridge between them. There are, however, certain limitations in the type of radical which could be involved; first, it could not contain groups which are titrated in the pH range examined in this investigation, since the back-titration curve shows no liberation of such groups and is moreover almost identical with the titration curve of the acid or alkali treated samples (Figs. 4 and 5), and secondly, the stability

to acid and alkali of the links involving the amino- and the hydroxyl groups would have to be very similar. In our opinion these restrictions make the preceding explanation of the observed behaviour improbable, and a simpler and preferable explanation is that in which the amino- and the hydroxyl groups are linked by hydrogen bonds. Bonding of this type has frequently been suggested as being important in protein structure, and our observations on the behaviour of deoxypentose nucleic acid resemble in some respects those recorded for egg albumen (Cannan, Kibrick, and Palmer, *Ann. N.Y. Acad. Sci.*, 1941, **41**, 243; Crammer and Neuberger, *Biochem. J.*, 1943, **37**, 302), which have been interpreted by postulating a hydrogen bond between a phenolic hydroxyl group and a carboxylate ion. Although it is undesirable at the present stage to speculate too far as to the macromolecular structure of deoxypentose nucleic acid, a hydrogen bond between an amino-group and either the -NH- group or the enolic -C(OH)- group of an adjacent guanine or thymine radical could explain satisfactorily our experimental results. The large number of such bonds which are possible, the maximum number being two for every four atoms of phosphorus, would give a degree of stability to the untreated deoxypentose nucleic acid, and in order to degrade the nucleic acid it might be necessary to break many of the hydrogen bonds simultaneously. Such a process would lead to an abnormal titration curve of the type shown in Fig. 1. It is not possible on the basis of these data to decide whether the hydrogen bonds unite nucleotides in the same, or in different chains; this aspect is considered in the light of viscosity and streaming birefringence by Creeth, Gulland, and Jordan (*loc. cit.*).

The increase in viscosity observed at approximately pH 7 when a solution of the nucleic acid was adjusted to that value after treatment with acid or alkali (Vilbrandt and Tennent, *loc. cit.*; Creeth, Gulland, and Jordan, *loc. cit.*) does not involve the blocking of the amino- and the enolic hydroxyl groups, since the titration curves obtained were identical with the back-titration curve shown in Fig. 1 whether the solution was titrated immediately or was allowed to remain at approximately pH 7 for 96 hours in the absence of atmospheric oxygen. During this period the viscosity had risen to a value of the same order as that observed with the original acid (Creeth, Gulland, and Jordan, *loc. cit.*).

A different behaviour was observed in samples which had been precipitated by alcohol at pH 7 after acid or alkaline treatment. Some blocking of the enolic hydroxyl groups occurred (Figs. 4 and 5), but to a much smaller extent than that found with the original material, and the properties of the precipitated material appeared to be independent of the viscosity changes, since very similar titration curves were obtained whether the product was precipitated immediately or after 96 hours. Precipitation would thus seem to be the important factor. There is no evidence from titration data that precipitation effects blocking of the amino-groups.

Greenstein and Jenrette (*J. Nat. Cancer. Inst.*, 1940, **1**, 77; *Cold Spring Harbor Symp. Quant. Biol.*, 1941, **9**, 236) have postulated on the evidence of viscosity measurements that reversible depolymerisation of thymus deoxypentose nucleic acid takes place on the addition of neutral salts. Titration of the sodium salt of thymus deoxypentose nucleic acid in $\text{M-potassium chloride}$ (Fig. 2) and in 2.53 molar guanidine sulphate (Fig. 3) showed that the changes in viscosity which occur bear no relation to the irreversible change which takes place on treatment with acid or alkali, since the discrepancy between the forward- and back-titration curves was still present in these salt solutions. The lowering of the viscosity by the addition of salt must therefore involve a different type of physico-chemical change to that occurring on treatment with acid or alkali.

EXPERIMENTAL.

Apparatus.—The electrometric titrations were carried out according to the method described by Fletcher, Gulland, and Jordan (*loc. cit.*), and the titration curves were corrected for the titration of water at the extremes of pH by the method of Jordan and Taylor (*loc. cit.*). The solutions for titration contained 100 to 200 mg. of the samples in 20 ml. of water.

Preparation of Alkali-treated Samples of the Sodium Salt of Thymus Deoxypentose Nucleic Acid.—To a solution of sodium salt of deoxypentose nucleic acid (2 g.) in water (100 ml.), 0.5N-sodium hydroxide (25 ml.) was added with mechanical stirring. The solution then had a reaction of pH 12.30. 0.5N-Hydrochloric acid (24 ml.) diluted with water (51 ml.) was added slowly with rapid stirring to avoid precipitation. The pH was finally adjusted to 7.0. The solution was added immediately or at the time required to ethyl alcohol (750 ml.). The white granular precipitate (1.6 g.) was collected, washed with alcohol, and dried in a vacuum over phosphoric oxide.

Preparation of Acid-treated Samples of the Sodium Salt of Thymus Deoxypentose Nucleic Acid.—To a solution of the sodium salt of deoxypentose nucleic acid (2 g.) in water (150 ml.), 0.08N-hydrochloric acid (50 ml.) was added slowly with constant stirring, the final reaction being pH 3.1. 0.195N-Sodium hydroxide (24 ml.) was added slowly with stirring, and the reaction adjusted to pH 7.1 with dilute hydrochloric acid. The solution was added immediately or later as required to ethyl alcohol (750 ml.).

The white granular precipitate (1.6 g.) was collected, washed with alcohol, and dried in a vacuum over phosphoric oxide.

Preparation of Barium Thymate.—A solution of the sodium salt of thymus deoxypentose nucleic acid (15 g.) in water (400 ml.) was warmed to 80° and mixed with 10% sulphuric acid (30 ml.) at the same temperature. A white solid formed and redissolved in 5 minutes. The solution was maintained at 80° for 30 minutes. Silver sulphate (5 g.) was added and the suspension shaken for 1 hour, cooled in water and then to 0°, and mixed with a solution of barium acetate (20 g.) and barium chloride (5 g.) in water (30 ml.). Next day the supernatant was decanted, and the solid collected by centrifuge and washed repeatedly with 90% alcohol and then with 100% alcohol and ether. The product (4.6 g.) was dried in a vacuum over phosphoric oxide.

Analyses.—All samples were dried at 110° in a vacuum over phosphoric oxide. Details of the analytical methods are given in Part I (*loc. cit.*). Sodium salt of deoxypentose nucleic acid of calf thymus prepared by Professor Caspersson and deproteinised by us (see text), found: C, 35.5; H, 4.14; N, 15.4; P, 9.4; Na, 7.2 (colorimetric)%. Alkali-treated sodium salt of deoxypentose nucleic acid of calf thymus (respective values for three preparations), found: C, 35.3, 35.7, 36.1; H, 3.62, 3.83, 3.79; N, 15.4, 15.6, 15.5; P, 9.30, 9.63, 9.58; Na, —, 6.42, 6.28 (gravimetric)%. Acid-treated sodium salt of deoxypentose nucleic acid of calf thymus, found: C, 35.9; H, 3.76; N, 15.8; P, 9.41; Na, 6.33 (gravimetric)%. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine, adenine, cytosine, and thymine deoxypentose nucleotides, *i.e.* $(C_{29}H_{45}O_{24}N_{15}P_4Na_4)_x$, the additional HONa of the terminal groups being ignored: C, 35.4; H, 3.4; N, 15.9; P, 9.4; Na, 6.95%. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine and thymine, and 1.2 mols. of cytosine and 0.8 mol. of adenine deoxypentose nucleotides, *i.e.* $(C_{38.8}H_{45}O_{24.2}N_{14.6}P_4Na_4)_x$, the additional HONa of the terminal groups being ignored: C, 35.4; H, 3.4; N, 15.5; P, 9.4; Na, 6.98%.

Barium thymate (respective values for two preparations), found: C, 27.1, —; H, 3.46, —; N, 5.44, 5.53; P, 9.47, 9.44; Ba, 23.3, 23.1%. Calc. for a molecule containing four atoms of phosphorus, 1.2 mols. of cytosine, 1.0 mol. of thymine, 2.22 atoms of barium and a terminal OH group to every five atoms of phosphorus, *i.e.*, $C_{29.4}H_{40.7}O_{25.8}N_{5.6}P_4Ba_{2.22}$: C, 26.9; H, 3.10; N, 5.96; P, 9.44; Ba, 23.2%. Calc. for a molecule containing four atoms of phosphorus, 1.0 mol. each of cytosine, and thymine, 2.22 atoms of barium, and a terminal OH group to every five atoms of phosphorus, *i.e.*, $C_{29}H_{40.1}O_{25.8}N_5P_4Ba_{2.22}$: C, 26.8; H, 3.08; N, 5.37; P, 9.56; Ba, 23.4%.

It is a pleasure to record our thanks to Imperial Chemical Industries Ltd. for the loan of apparatus; to Professor W. T. Astbury, F.R.S., for the gift of the sample prepared by Professor Caspersson; to Mr. J. M. Creeth, B.Sc., for preparing two of the alkali-treated samples, for preliminary work on the acid treated material, and for some of the sodium analyses; to Mr. C. J. Threlfall, B.Sc., for preparing the samples of barium thymate; and to Mr. J. E. Still, B.Sc., and Mr. D. S. R. Cameron for the microanalyses.

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[Received, November 2nd, 1946.]

214. Deoxypentose Nucleic Acids. Part III. Viscosity and Streaming Birefringence of Solutions of the Sodium Salt of the Deoxypentose Nucleic Acid of Calf Thymus.

By J. M. CREETH, J. MASSON GULLAND, and D. O. JORDAN.

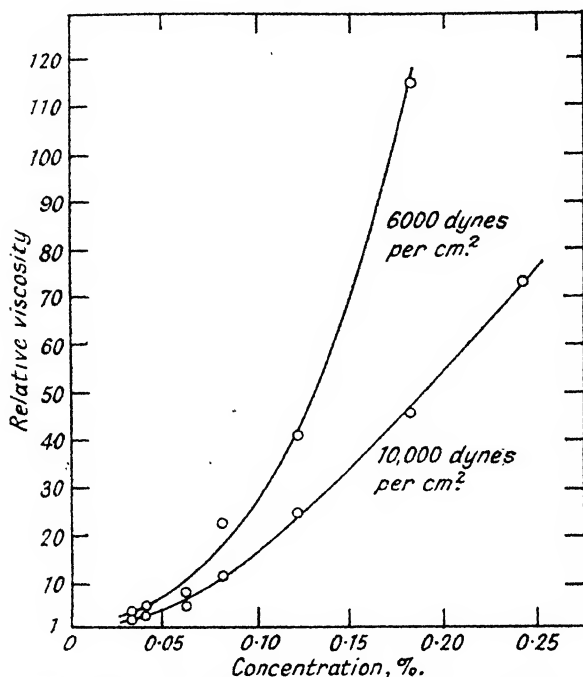
The high viscosity and marked streaming birefringence of solutions of the tetrasodium salt of deoxypentose nucleic acid of calf thymus are found to remain constant between pH 5.6 and 10.9. Outside these critical limits the viscosity falls to a very low value and the streaming birefringence disappears, but they increase again if the pH is readjusted to 7.0. The critical pH values are coincident with those at which a liberation of amino- and enolic hydroxyl groups has been observed (Gulland, Jordan, and Taylor, Part II, this vol., p. 1131) and it is considered that the two phenomena are related and are due to the fission of the hydrogen bonds postulated as linking the purine-pyrimidine hydroxyl groups and some of the amino-groups. The present data do not show whether bonding of neighbouring polynucleotide chains or of nucleotides in the same chain is involved.

The viscosities of solutions of the tetrasodium salt of deoxypentose nucleic acid of calf thymus were reduced considerably by low concentrations of neutral salt, increase of the concentration above 0.01M having relatively only a small effect on the viscosity.

THE high viscosity exhibited by aqueous solutions of the sodium salt of thymus deoxypentose nucleic acid at pH 7.0 has been shown to decrease with the addition of acid and alkali (Jones and Austrian, *J. Biol. Chem.*, 1907, 3, 1; Jones, *ibid.*, 1908, 5, 1; Hammarsten, *Biochem. Z.*, 1924, 144, 383; Vilbrandt and Tennent, *J. Amer. Chem. Soc.*, 1943, 65, 1806) and with the addition of neutral salts (Greenstein and Jenrette, *J. Nat. Cancer Inst.*, 1940, 1, 77; *Cold Spring Harbor Symp. Quant. Biol.*, 1941, 9, 236). A mechanism involving depolymerisation has been ascribed to both these processes (Greenstein and Jenrette, *loc. cit.*; Vilbrandt and Tennent, *loc. cit.*). In view of the observations (Gulland, Jordan, and Taylor, Part II, *loc. cit.*) that

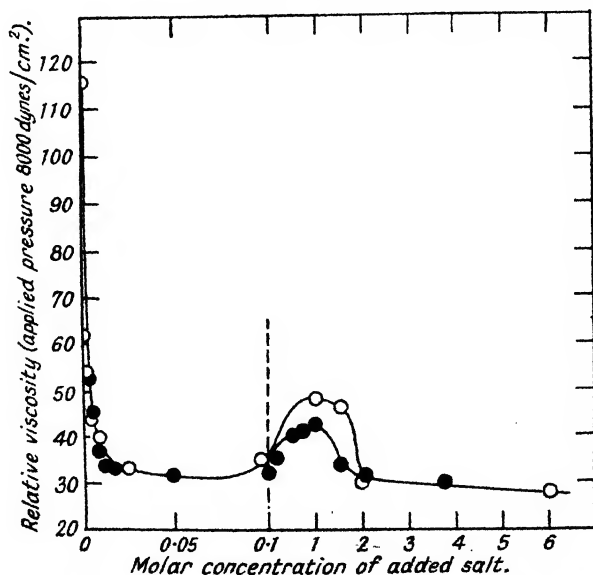
treatment with acid or alkali of solutions of the sodium salt of thymus deoxypentose nucleic acid prepared by Gulland, Jordan, and Threlfall (Part I, this vol., p. 1129) leads to the liberation

FIG. 1.



The variation of the viscosity of solutions of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus with concentration at two different pressures.

FIG. 2.



The variation of the viscosity of solutions of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus with concentration of added salt.

Sodium chloride ●; guanidine chloride ○.

of titratable groups, whereas the addition of neutral salts does not, an investigation of the viscosity of solutions of this preparation of this nucleic acid appeared desirable.

Results of this Investigation.—The viscosity of aqueous solutions of this preparation of the sodium salt of thymus deoxypentose nucleic acid increased considerably with rise of concentration (Fig. 1), and the viscosity of a 0.5% solution could not be measured in the capillary viscometers used in this investigation. At all concentrations studied the viscosity varied with the applied pressure, thus being abnormal or structural in character.

The magnitude of the relative viscosity was very much greater than that recorded for other preparations of the sodium salt of this nucleic acid. Thus, the relative viscosity of our material at pH 7.0 in 0.243% solution at 25°, measured in a capillary viscometer at 8000 dynes/cm.², was 116, whereas from measurements with the sodium salt prepared by the method of Bang (Hofmeister's "Beiträge Chem. Physiol. Path.", 1903, 4, 331) and Hammarsten (*loc. cit.*), Vilbrandt and Tennent (*loc. cit.*) record 5.7 for a 0.3% solution at 25° measured in an Ostwald viscometer, and Greenstein and Jenrette (*loc. cit.*) give 5.53, a limiting value at high pressures, for a 0.25% solution at 25° measured in a capillary viscometer.

The addition of sodium chloride or guanidine chloride (the guanidinium ion being specified as most effective by Greenstein and Jenrette) lowered very considerably the relative viscosities of solutions of the sodium salt of thymus deoxypentose nucleic acid (Fig. 2). The viscosity fell rapidly at first as the salt concentration was increased, reaching a critical value at about 0.01M with both sodium chloride and guanidine chloride. On increasing the concentration above the critical value only comparatively small changes in viscosity occurred; a rise to a slight peak and subsequent fall were observed at approximately 1M, a result which may be compared with that observed by Needham, Kleinzeller, Miall, Dainty, Needham, and Lawrence (*Nature*, 1942, 150, 46) for the action of neutral salts on the viscosity of solutions of myosin.

The variation of the viscosity with the pH of the solution is shown in Fig. 3; the ionic strength was maintained at 0.01 throughout. The relative viscosity remained constant as the pH was varied from 5.6 to 10.9, but outside these limits it fell rapidly, and at pH 12.08 and at pH 3.38 the viscosity of the solutions no longer varied with the applied pressure. These results are not in agreement with the data recorded by Vilbrandt and Tennent (*loc. cit.*) who observed a maximum in the relative viscosity at pH 7.0 and a gradual reduction of the relative viscosity as the pH was changed in either direction from neutrality. The results of these authors resemble those obtained by us with samples of the original sodium salt of thymus deoxypentose nucleic acid which had been treated with alkali at pH 12.5 or with acid at pH 3.5 and then precipitated by the addition of ethyl alcohol at pH 7.0 (Fig. 3). Our results with the acid- or alkali-treated material also closely resemble those obtained with a sample of the sodium salt supplied by Professor Caspersson through Professor Astbury in 1939, and prepared by the Hammarsten-Bang procedure.

The data for the streaming birefringence of solutions of the sodium salt of thymus deoxypentose nucleic acid are recorded in the table, and followed closely the changes in viscosity. In agreement with the experimental results of Greenstein and Jenrette (*J. Nat. Cancer Inst.*, 1940, 1, 77, Table 2) and the conclusions of Snellmann and Widström (*Arkiv Kemi, Min. Geol.*, 1945, 19, A, No. 31) solutions of our deoxypentose nucleic acid showed considerable streaming birefringence in the presence of a high concentration (4M) of neutral salt (see table).

Variation with pH (ionic strength maintained at 0.01 throughout) and with concentration of sodium chloride of the streaming birefringence of 0.243% solution of the sodium salt of thymus deoxypentose nucleic acid.

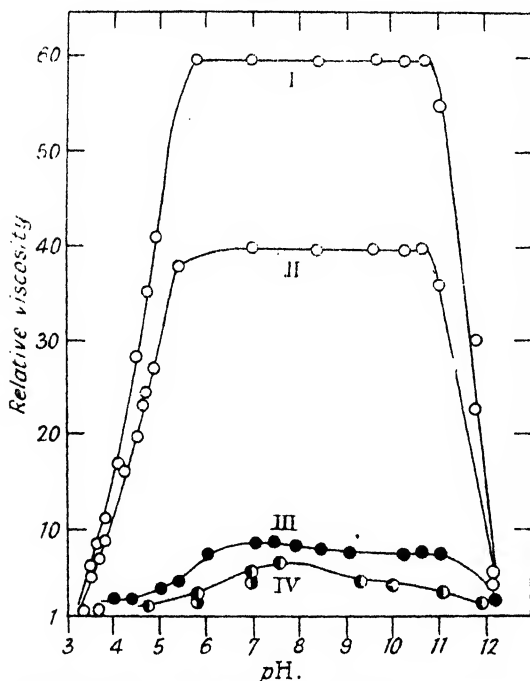
pH	3.7	4.0	4.3	5.0	10.0	10.9	12.0
		to	to	to	to	to	
		4.3	5.0	10.0	10.7	11.6	
Streaming birefringence (relative values on arbitrary scale)	0	1	2	3	2	1	0
Original nucleic acid, in water at pH 6.9, 4; in 4M-sodium chloride, 2.							

The action of acid and alkali in reducing the viscosity of solutions of the sodium salt of thymus deoxypentose nucleic acid has been shown by Vilbrandt and Tennent (*loc. cit.*) to be to some extent reversible if the solutions are returned to pH 7.0. We have confirmed this result, but have observed that the regain of high viscosity after acid treatment is different from that which occurs after alkaline treatment. When a 0.243% solution was left at pH 12.5 for 15 minutes and then returned to pH 7.0, the viscosity increased steadily with time (Fig. 4) and

moreover regained its structural character; after 91 hours the relative viscosity had increased to a value of the same order as that of the original acid, but the variation with applied pressure was somewhat different, the viscosity being lower at high pressures and higher at low pressures (Fig. 4). With concentrations of the sodium salt of deoxypentose nucleic acid up to 0.5% there was no appreciable increase in the viscosity at pH 7.0 after treatment at pH 3.5 for 15 minutes, but a 1.0% solution after such treatment gelled on standing for 12 hours.

When the products of alkali- or acid-treatment were precipitated at pH 7.0 by the addition of ethyl alcohol, isolated, dried, and redissolved in water, they showed only a slight increase in viscosity with lapse of time. A marked difference exists, therefore, between the behaviour of precipitated and non-precipitated material after alkali- or acid-treatment.

FIG. 3.



The variation of the viscosity of solutions of various specimens of deoxypentose nucleic acid.

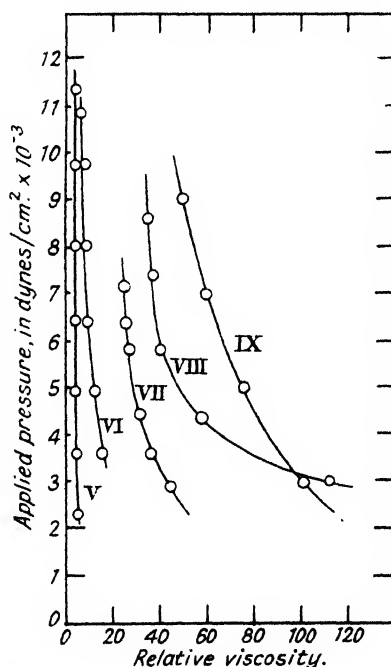
Tetrasodium salt of deoxypentose nucleic acid of calf thymus, \circ :

I (applied pressure 3000 dynes/cm.²), II (applied pressure 7000 dynes/cm.²).

Tetrasodium salt of deoxypentose nucleic acid after alkaline treatment, III, \bullet ; after acid treatment, IV, \circ .

Tetrasodium salt of deoxypentose nucleic acid of calf thymus supplied by Professor Caspersson, IV, \bullet .

FIG. 4.



Increase of viscosity of a solution of the tetrasodium salt of deoxypentose nucleic acid on standing at pH 7.0 after alkaline treatment: V, after 25 mins.; VI, after 18 hours; VII, after 42 hours; VIII, after 91 hours; IX, original solution of tetrasodium salt of deoxypentose nucleic acid.

Discussion.—The results of the viscosity measurements are interpreted qualitatively in view of the fact that the viscosity was not a function of the concentration alone over the range of concentration studied, and for such examples the theoretical treatment of viscosity data is very incomplete (Eirich, *Rep. Prog. Physics*, 1940, 7, 329). Signer, Caspersson, and Hammarsten (*Nature*, 1938, 141, 122) have applied one of the formulæ relating viscosity with the size and shape of the molecule, but we have not felt entitled to adopt such procedure in view of the much greater structural viscosity of solutions of our material as compared with that of the sample supplied by Professor Caspersson.

The evidence obtained by electrometric titration (Gulland, Jordan, and Taylor, *loc. cit.*) suggests that in the original nucleic acid hydrogen bonds exist between the amino- and hydroxyl groups of nucleotides, and that these bonds are broken at reactions more acid than pH 5 and

more alkaline than pH 11. The addition of acid or alkali did not lower the viscosity of solutions of deoxypentose nucleic acid until these critical pH values were reached.

The reduction in viscosity and in streaming birefringence could be explained by the rupture of hydrogen bonds between adjacent chains, producing units of lower molecular weight and greater symmetry. It is also conceivable that a rolling-up of a single polynucleotide chain could occur, following the fission of hydrogen bonds between nucleotides in that chain, thus reducing the molecular asymmetry but not the molecular weight. The present data do not reveal which of these alternatives is correct or whether both processes occur.

It is most improbable that when a solution of the sodium salt of deoxypentose nucleic acid is restored to pH 7 after acid or alkaline treatment, aggregation will produce precisely the same structure as existed in the original nucleic acid micelle, and it is likely that water molecules will play a greater part in the structure of the new micelle. Subsequent precipitation of the material at pH 7.0 by the addition of ethyl alcohol, followed by drying of the product, may thus considerably alter the structure of the micelle, and it is not surprising therefore that in solution the material isolated by precipitation behaved differently from the non-precipitated product.

The decrease in viscosity on the addition of sodium chloride cannot have been caused by a disaggregation of the type described above, since no titratable groups were produced (Gulland, Jordan, and Taylor, *loc. cit.*). At least three explanations of this decrease are possible, a disaggregation of coarse aggregates of micelles, a change in the shape of the micelle, or a change in the structure of the ion atmosphere and the hydrosphere. The data so far obtained do not permit a choice between these alternatives.

EXPERIMENTAL.

The determination of viscosity was made in a viscometer similar to that described by Frampton (*J. Biol. Chem.*, 1939, **129**, 233). Four viscometers were employed, having capillaries 14.6, 13.4, 14.5, and 12.0 cm. long and the following radii: 0.0390, 0.0476, 0.0575, and 0.0965 cm. respectively. The time for the liquid meniscus to fall between two marks etched on the upright tubes at a known distance apart (*ca.* 0.5 cm.) was measured with a stop watch, reading in 1/10 secs., the meniscus being followed by a travelling microscope. In the experimental results recorded in the figures, the geometric means of the initial and final hydrostatic pressures, between which the viscosity was determined, are recorded.

Streaming birefringence was determined by stirring mechanically a solution placed in a small cell on the stage of a polarising microscope.

The preparation of the materials employed has been described in Parts I and II (this vol., pp. 1129, 1131)

It is a pleasure to record our thanks to the British Empire Cancer Campaign for a maintenance grant to one of us (J. M. C.) and for defraying a part of the expenses of this investigation, and to Imperial Chemical Industries Ltd. for the loan of apparatus.

UNIVERSITY COLLEGE, NOTTINGHAM.

[Received, November 2nd, 1946.]

215. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part III. Diacetylenedicarboxylic Acid Dihydrate.*

By J. D. DUNITZ and J. MONTEATH ROBERTSON.

The crystal and molecular structure of diacetylenedicarboxylic acid dihydrate, $\text{HO}_2\text{C}\cdot\text{C}\equiv\text{C}\cdot\text{C}\equiv\text{C}\cdot\text{CO}_2\text{H}\cdot 2\text{H}_2\text{O}$, has been determined from X-ray data, and is shown to be similar in general outline to that of oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate (Parts I and II, this vol., pp. 142, 148). A network of hydrogen bridges extends throughout the crystal and links the water molecules (or oxonium ions) to the adjoining acid molecules.

In the present crystal there is, however, a space-group change, from C_{2h}^2 to C_{2h}^1 , and the molecules possess a two-fold axis of symmetry instead of a centre. The configuration is no longer coplanar, the carboxyl groups at opposite ends of the molecule lying nearly in two planes inclined to one another at about 57° .

The bond distances within the molecule are shown in Fig. 3, and should be accurate to within about ± 0.05 Å., except in the carbon chain [C(2)–C(1) and C(1)–C(1')] where a considerably higher accuracy of about ± 0.02 Å. should apply. The central single bond of 1.33 Å. is the shortest formal single bond so far discovered. This result is discussed, and also the question of whether the carbon-carbon triple bond in acetylene itself is really a suitable standard for the "normal" triple bond type.

In previous papers (*loc. cit.*) we have discussed the structure of oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate and shown that they are of the same type. The two water molecules (or oxonium ions) are situated between the carboxyl groups of adjoining acid molecules, to which they are bound by one very strong and two rather weaker types of hydrogen

bridge. These connections form a spiral network which extends throughout the crystal and confers considerable stability on the whole structure. In these crystals the acid molecules possess a centre of symmetry, the carboxyl groups are nearly symmetrical, and the whole molecule is either planar or very nearly so, as would be expected from general chemical evidence.

We have now completed a similar detailed study of diacetylenedicarboxylic acid dihydrate. In this structure there is a space-group change, from $C_{2h}^5(P2_1/a)$ to $C_{2h}^6(I2/c)$ and a consequent doubling of the c axis. At first sight, and indeed in the principal projection of the structure (Fig. 1), the whole arrangement appears to be entirely analogous to that of the other two structures, apart from the lengthened carbon chain and the c axis doubling. The analysis of the principal zone, ($h0l$), offers no particular difficulty, and proceeds on the same lines as before. In attempting to explain the intensities of other zones of reflections, however, serious difficulties were encountered. These could only be resolved on the assumption that the molecule of diacetylenedicarboxylic acid does not contain a symmetry centre and that the two carboxyl groups are not coplanar but lie in two planes inclined to one another at about 57° . The opposite ends of the molecule are related by a two-fold axis of symmetry which passes through its centre. In Fig. 1 the projection of this two-fold axis gives rise to a centre of symmetry and makes this picture precisely analogous to those already described for the other structures.

This change in configuration is difficult to understand, particularly as the bond-length measurements indicate that resonance effects extend throughout the molecule and these should tend to produce a coplanar form. As discussed more fully below, the configuration adopted in this case appears to be governed by the strongly directed intermolecular hydrogen bridging which exists in the crystal.

Apart from these curious effects, this structure is of special interest in providing fairly reliable measurements on a system of conjugated triple bonds. The linear carbon chain lies in the (010) plane, and two-dimensional Fourier methods provide excellent resolution of the various atoms. Both the triple bonds and their connecting link are found to be somewhat shorter (Fig. 3) than previous measurements on other compounds have indicated. These facts are discussed more fully below after the structure has been described.

Description of the Structure.—*Crystal data.* Diacetylenedicarboxylic acid dihydrate, $C_6H_2O_4 \cdot 2H_2O$; M , 174.1; m. p. (decomp. with charring) $95-100^\circ$; d , calc. 1.43, found 1.43—1.45; monoclinic prismatic, $a = 11.15 \pm 0.03$, $b = 3.75 \pm 0.01$, $c = 20.18 \pm 0.08$ Å., $\beta = 107.0^\circ \pm 0.5^\circ$. Absent spectra, (hkl) when $h + k + l$ is odd; ($h0l$) when either h or l is odd. Space-group, $C_{2h}^4(Ic)$ or $C_{2h}^6(I2/c)$. (C_{2h}^6 assumed in this analysis.) Four molecules per unit cell. Molecular symmetry, centre or two-fold axis. (Two-fold axis assumed in this analysis.) Volume of unit cell, 806.7 Å.³. Absorption coefficient for X-rays, $\lambda = 1.54$, $\mu = 13.4$ cm.⁻¹. Total number of electrons per unit cell = $F(000) = 360$.

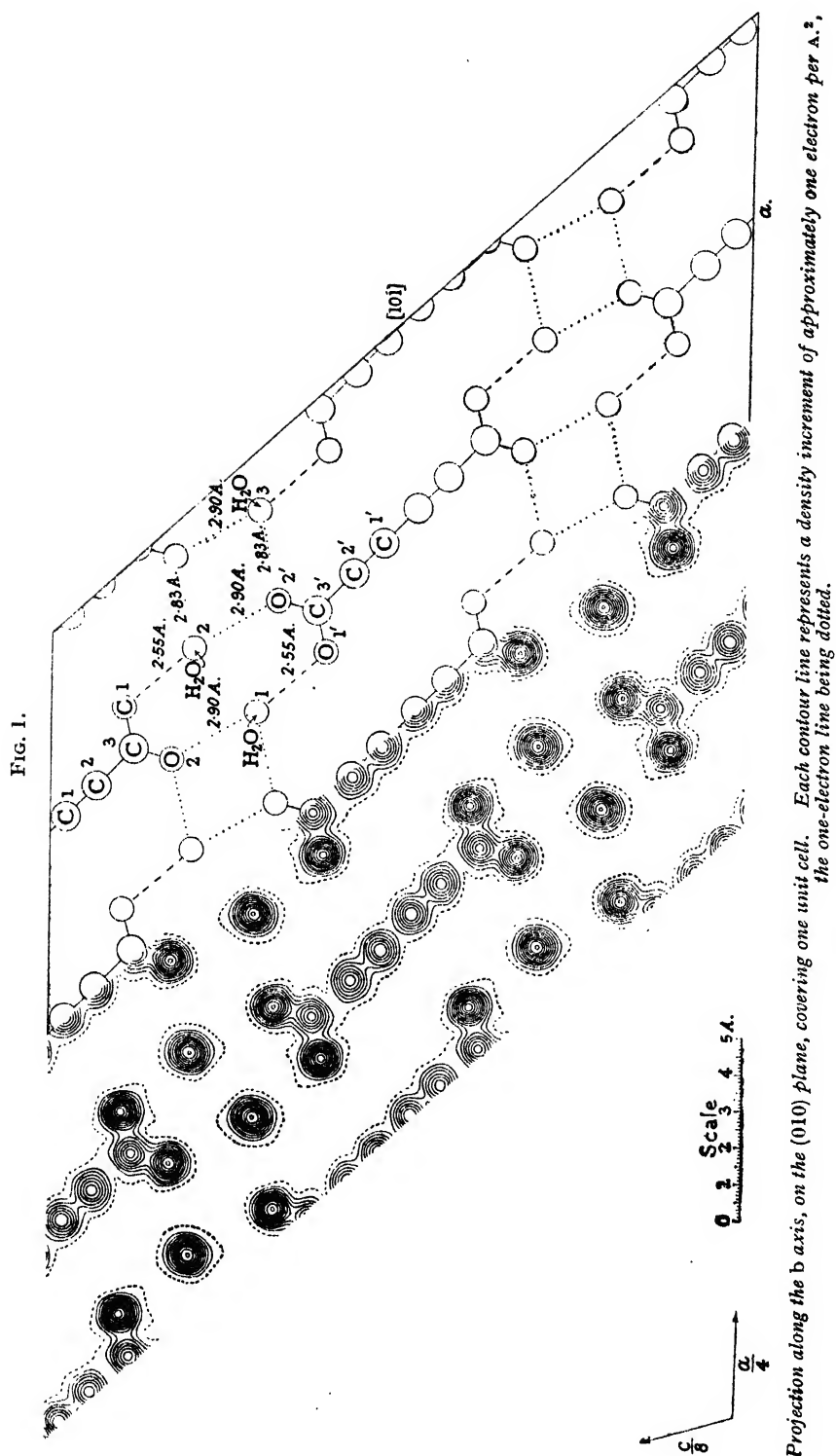
Diacetylenedicarboxylic acid was first prepared by Baeyer (*Ber.*, 1885, 18, 676, 2270) and his method of preparation was followed. Our final product, however, was not identical with that obtained by Baeyer, his being described as the monohydrate while ours was without doubt the *dihydrate*.

Crystals were obtained from water as small, faintly pink or yellow, sword-like needles, elongated in the b -axis direction. The (001) face was always prominently developed and the (101) also appeared, other faces being generally absent. The crystals deepen in colour when exposed to light, becoming purple and eventually black; exposure to X-rays causes them to become quite black almost immediately.

Structure analysis. The dimensions of the unit cell compared with oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate suggested that the main features of the structure were the same as in these two compounds (see Table I, Part I, *loc. cit.*). The inclination of the [101] axis to the a axis is still about 50° and the increase in its half-length (the c axis is doubled) as compared with acetylenedicarboxylic acid dihydrate (2.55 Å.) is again just about the amount required to accommodate an extra pair of carbon atoms.

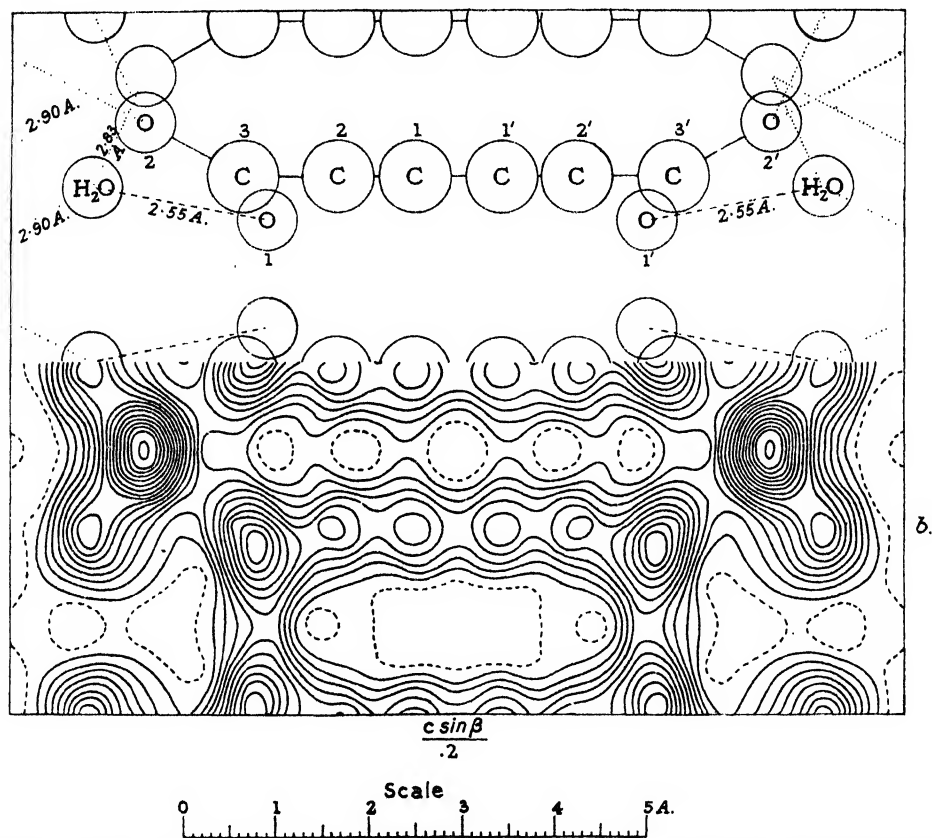
A trial model set up on the assumption that the long axis of the molecule was lying along [101] with the planes of the carboxyl groups inclined at about 30° to the (010) plane gave good agreements for the observed ($h0l$) intensities. The x and z co-ordinates were then refined by two successive Fourier syntheses, giving projections on the (010) plane. The final projection is shown in Fig. 1, from which accurate values of these co-ordinates can be obtained.

To determine the y co-ordinates in the structure, it is necessary to decide between certain alternative arrangements that are possible in the space-group C_{2h}^6 . The centres of the molecules must lie on special positions, but these may be (a) the centres of inversion on the glide plane a , (b) the centres of inversion on the glide plane c , (c) the two-fold rotation axes. This choice of



origins does not affect the projection on (010) described above, but it does affect the general planes and especially the $(0kl)$ structure factors, which were next examined in detail. Alternative (a) was eliminated by trial methods, and as (b) seemed much more likely than (c), by analogy with the previous structures, this possibility was examined in considerable detail. It was not possible to obtain good agreements between the calculated and the observed structure factors, the mean discrepancy always being about 30%. A Fourier projection was made, using terms whose sign seemed reasonably certain, but this projection was unsatisfactory and did not lead to any further refinement of the assumed co-ordinates. The idea of a molecular centre of symmetry was therefore abandoned, and possibility (c) was next explored. A two-fold rotation axis permits new molecular configurations and it was soon found that a

FIG. 2.



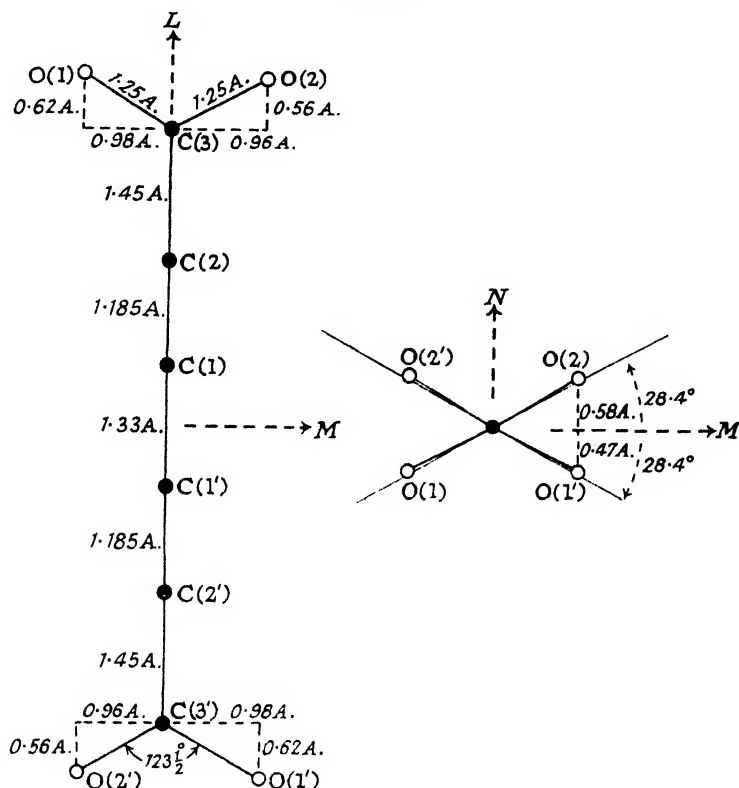
Projection along the a axis, covering half a unit cell. The centres of the molecules are situated on rotation axes, at 0.11 Å. from the glide plane c . Contour scale as in Fig. 1, except that the two-electron line is dotted.

model, consistent with the projection in Fig. 1, but with the planes of the carboxyl groups oppositely inclined, each at about 30° to (010), led to greatly improved agreements for the $(0kl)$ and general structure factors, the mean discrepancy being reduced to less than 20%. The y co-ordinates were then refined by Fourier projections along the a axis, and the final diagram is shown in Fig. 2. The resolution of the atoms in Fig. 2 is not very complete, and it will be seen from the explanatory diagram that considerable overlapping must be expected. It is nevertheless possible to assign y co-ordinates which account fairly well for the shape of the contours. These co-ordinates are rather less certain than the x and z co-ordinates, especially for the atoms C(3), O(1), O(2), and H_2O .

Molecular dimensions and co-ordinates. The x and z crystal co-ordinates obtained from the final Fourier projection on (010) are shown in Fig. 5, and are listed, together with the y co-ordinates, in Table I. These co-ordinates lead to the molecular model given in Fig. 3 and

to the intermolecular distances of Fig. 1. The orientation of the molecule in the crystal is given in Table II, the molecular axis L being the direction of the carbon chain, N the direction of the two-fold rotation axis, and M the normal to the LN plane. Molecular co-ordinates referred to these axes are given in Table III.

FIG. 3.



Dimensions of the diacetylenedicarboxylic acid molecule. Projections of the molecule are drawn on the LM and MN planes.

TABLE I.

Observed co-ordinates. Centre of symmetry on glide plane c as origin; x, y, z are referred to monoclinic crystal axes a, b, c ; x', y, z' are referred to the a and b crystal axes and their perpendicular c' .

Atom (cf. Fig. 1).	$x, \text{\AA.}$	$y, \text{\AA.}$	$z, \text{\AA.}$	$x', \text{\AA.}$	$z', \text{\AA.}$	$\frac{2\pi x}{a}$	$\frac{2\pi y}{b}$	$\frac{2\pi z}{c}$
C(1)	0.332	0.11	4.555	-0.999	4.355	10.7°	10.5°	81.3°
C(2)	0.920	0.11	3.687	-0.157	3.525	29.7	10.5	65.8
C(3)	1.642	0.11	2.625	0.875	2.51	53.0	10.5	46.8
O(1)	2.856	-0.36	2.899	2.009	2.772	92.2	34.6	51.7
O(2)	1.046	0.69	1.503	0.607	1.436	33.8	65.4	26.8
H ₂ O	3.945	0.00	0.920	3.676	0.880	127.4	0	16.4
Centre of molecule ...	0	0.11	5.045	-1.475	4.824	0	10.5	90.0

TABLE II.

Orientation of the molecule in the crystal. The symbols $\chi_L, \psi_L, \omega_L; \chi_M, \psi_M, \omega_M; \chi_N, \psi_N, \omega_N$ have the same meanings as in Part II, Table II.

$\chi_L = -44.5^\circ$	$\cos \chi_L = 0.7133$	$\chi_M = -134.5^\circ$	$\cos \chi_M = -0.7009$	$\chi_N = 90^\circ$	$\cos \chi_N = 0$
$\psi_L = 90^\circ$	$\cos \psi_L = 0$	$\psi_M = 90^\circ$	$\cos \psi_M = 0$	$\psi_N = 0^\circ$	$\cos \psi_N = 1$
$\omega_L = -134.5^\circ$	$\cos \omega_L = -0.7009$	$\omega_M = 135.5^\circ$	$\cos \omega_M = -0.7133$	$\omega_N = 90^\circ$	$\cos \omega_N = 0$

TABLE III.

Co-ordinates referred to orthogonal molecular axes L , M , N . The origin of these co-ordinates is situated in the crystal at $x = 0$, $y = 0.11$ Å., $z = 5.045$ Å. ($c/4$).

	L , Å.	M , Å.	N , Å.		L , Å.	M , Å.	N , Å.
C(1)	0.665	0	0	O(1)	3.92	-0.98	-0.47
C(2)	1.85	0	0	O(2)	3.86	0.96	0.58
C(3)	3.30	0	0				

Discussion of Results.—Hydrogen bonding and molecular configuration. Comparison of Fig. 1 with the corresponding projections for oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate (Part I, Fig. 1, and Part II, Fig. 1) shows that the same type of structure appears to exist in all three crystals. So far as the intermolecular hydrogen bonding is concerned, the three crystals are almost identical, the relevant distances in diacetylenedicarboxylic acid dihydrate being $O(1)-H_2O = 2.55$ Å., $O(2)-H_2O = 2.90$ Å. and 2.83 Å., almost exactly the same as in acetylenedicarboxylic acid dihydrate. The spiral arrangement described in Parts I and II is exactly reproduced in this compound, the apparently closed circuit $O(1), H_2O, O(2'), C(3'), O(1'), H_2O, O(2), C(3), O(1)$ being actually a spiral which returns to an atom one translation along the b axis from the original atom; the closed four-membered ring formed by the weaker bonds of $2.83, 2.90, 2.83, 2.90$ Å. is again exactly analogous to the previous cases.

The molecule of diacetylenedicarboxylic acid is, however, clearly different in its geometric configuration from those of oxalic acid and acetylenedicarboxylic acid, which possess a centrosymmetric coplanar structure; even in those structures postulated for oxalic acid with a central bond of the normal single-bond distance the essential planarity of the molecule is not doubted (Part I), although in some of its salts the oxalate group has been reported non-coplanar (Hendricks and Jefferson, *J. Chem. Physics*, 1936, 4, 102). The diacetylenedicarboxylic acid molecule is found to possess not a centre of inversion, but a two-fold rotation axis, and the carboxyl groups at opposite ends of the molecule do not lie in the same plane. If two planes are taken, passing through the linear carbon chain and oppositely inclined to the (010) or LM plane at an angle of 28.4° , the carboxyl groups lie one on each of these planes. (The observed co-ordinates show that the oxygen atoms of the carboxyl groups are actually at 0.05 Å. from these planes, but this deviation is probably not significant.)

The normal configuration for this molecule is almost certainly a coplanar one. A conjugated system of the type shown by diacetylenedicarboxylic acid should confer appreciable double-bond character on the single bonds, and the distances observed in the carbon chain, which are further discussed below, show that this is the case. In the absence of any distorting forces such as steric or similar effects, a coplanar structure therefore seems clearly indicated as being the most stable.

It is seen from Fig. 4(c) that a planar centrosymmetric molecule in the space group C_{2h}^2 would lead to a system of hydrogen bonding in the form of a closed circuit, different from that observed in oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate, where infinite spirals of hydrogen bonds occur. Now the structure shown in Fig. 4(c) is a possible structure, and the fact that it does not occur in the crystal shows that it must have a higher total energy than the structure of Fig. 4(b). The non-coplanar configuration for the molecule is, on the other hand, almost certainly of a higher energy than a coplanar configuration, and the energy difference between these two configurations must be more than compensated by the energy difference between the two possible systems of hydrogen bonding. It seems clear that intermolecular hydrogen bonding must be the governing factor in this type of crystal structure, and that it is sufficiently stable and invariant to cause appreciable distortion from the natural coplanar shape of the molecule.

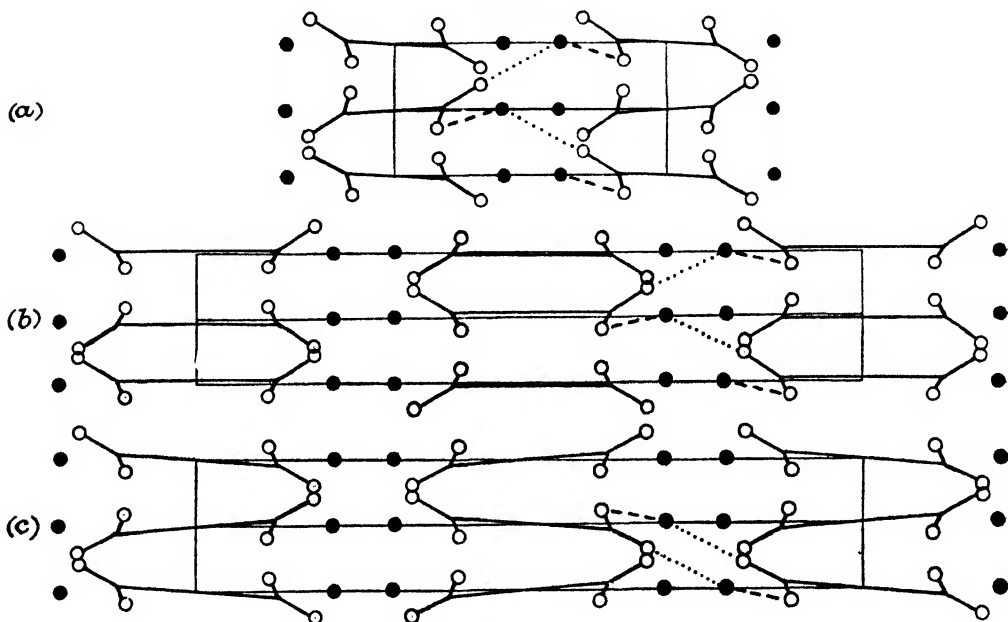
The strong directive power of hydrogen bonds has previously been noted as being able to preserve an open crystal structure which collapses, either partly as in resorcinol (Robertson and Ubbelohde, *Proc. Roy. Soc.*, 1938, A, 167, 122, 136) or completely as in ice, on breaking the bonds by heating. In diacetylenedicarboxylic acid dihydrate the directive power of the hydrogen bonds is sufficient to produce considerable distortion in the molecule itself. Such a directive power seems to indicate a certain amount of covalent character in the hydrogen bond.

The above argument may explain why the expected coplanar configuration for the molecule may not occur in the space-group C_{2h}^2 , but it gives no reason for the change in space-group from C_{2h}^2 in which the other compounds in this series occur. We would expect that the centrosymmetric planar molecule with an infinite spiral arrangement of the hydrogen bonds should exist in the space-group C_{2h}^2 with a lower energy than that of the structure observed.

Bond lengths within the molecule. In the carboxyl group we are again unable to distinguish between the carbon-oxygen bond lengths and find them both 1.25 Å. (In acetylenedicarboxylic acid dihydrate these bonds were 1.26 and 1.27 Å., and in oxalic acid dihydrate, 1.24 and 1.25 Å.; see Parts I and II.) The uncertainty here is of the same order as before, *viz.*, about 0.05 Å., but the three results taken together seem to indicate that the carbon-oxygen distances in the carboxyl group are probably equal, and support the view that the structures are likely to be ionic.

In the carbon chain the distance C(2)–C(3), measured as 1.45 Å., is also rather uncertain, but the fact that it is found to be slightly greater than the corresponding distance in acetylenedicarboxylic acid (1.43 Å.) may be significant. In the diacetylenedicarboxylic acid molecule the atoms no longer lie in one plane. The amount of double-bond character in the bond C(3)–C(2) must therefore be reduced with a consequent increase in the length of the bond.

FIG. 4.



(a) The acetylenedicarboxylic acid dihydrate structure.

(b) The diacetylenedicarboxylic acid dihydrate structure.

(c) A hypothetical diacetylenedicarboxylic acid dihydrate structure with a coplanar molecule in the space-group C_{2h}^2 .

These diagrams show one unit cell of the structures projected along the *a* axis. Oxygen atoms are shown as open circles, water molecules as black circles. For the sake of clarity only one hydrogen bond circuit (dotted lines) is shown in each case.

A considerably higher accuracy, probably to within about 0.02 Å., should apply to the remaining bond length measurements. The results are rather unusual, and for comparison Table IV shows the values which have been reported during the last few years for the various types of bond involved in triple-bonded systems.

We should expect bonds of the type $\equiv C-C\angle$ and $\equiv C-C\equiv$ to be considerably shortened from the normal single-bond distance of 1.54 Å., and the values found in the present investigation and for acetylenedicarboxylic acid are indeed much lower than 1.54 Å. The central bond of 1.33 ± 0.02 Å. is the shortest formal single bond yet reported, and it is, in fact, of just the length usually associated with a pure double bond. Accepting the value of 1.36 ± 0.03 Å. for this bond in diacetylene (Table IV), we might expect some further shortening in the present compound, due to the extra conjugation effects of the carboxyl groups. Wiebenga's value of 1.39 ± 0.03 Å. in diphenyldiacetylene seems rather high.

It should be noted that the general problem of contractions in triple-bonded systems has been given an alternative treatment by Conn, Kistiakowsky, and Smith (*J. Amer. Chem. Soc.*,

TABLE IV.

Bond-length measurements in triple-bonded systems.

[X-Ray = X-Ray crystal analysis. Sp. = Spectroscopic measurements. E.D. = Electron-diffraction measurements (vapours).]

Bond type.	Compound.	Bond distance, Å.	Reference.	Method.
$\equiv\text{C}-\text{C}\equiv$	Methylacetylene	1.462 ± 0.002	Herzberg, Patat, and Verleger, <i>J. Physical Chem.</i> , 1937, 41 , 123.	Sp.
		1.462 ± 0.002	Badger and Bauer, <i>J. Chem. Physics</i> , 1937, 5 , 594.	Sp.
		1.46 ± 0.02	Pauling, Springall, and Palmer, <i>J. Amer. Chem. Soc.</i> , 1939, 61 , 927.	E.D.
$\equiv\text{C}-\text{C}$	Dimethylacetylene	1.47 ± 0.02	do.	E.D.
	Dimethyldiacetylene	1.47 ± 0.02	do.	E.D.
	Tolan	1.40 ± 0.02	Robertson and Woodward, <i>Proc. Roy. Soc.</i> , 1938, <i>A</i> , 164 , 436.	X-Ray
	Diphenyldiacetylene	1.44 ± 0.03	Wiebenga, <i>Z. Krist.</i> , 1940, 102 , 193.	X-Ray
	Acetylenedicarboxylic acid	1.43 ± 0.04	This series, Part II.	X-Ray
	Diacetylenedicarboxylic acid	1.45 ± 0.05	This series, Part III.	X-Ray
$\equiv\text{C}-\text{C}\equiv$	Diacetylene	1.36 ± 0.03	Pauling, Springall, and Palmer, <i>loc. cit.</i>	E.D.
	Cyanogen	1.37 ± 0.02	do.	E.D.
	Dimethyldiacetylene	1.38 ± 0.03	do.	E.D.
	Diphenyldiacetylene	1.39 ± 0.03	Wiebenga, <i>loc. cit.</i>	X-Ray
	Diacetylenedicarboxylic acid	1.33 ± 0.02	This series, Part III.	X-Ray
$-\text{C}\equiv\text{C}-$	Acetylene	1.204 ± 0.002	Herzberg, Patat, and Spinks, <i>Z. Physik</i> , 1934, 92 , 87.	Sp.
	Methylacetylene	1.20 ± 0.03	Pauling, Springall, and Palmer, <i>loc. cit.</i>	E.D.
	Dimethyldiacetylene	1.20 ± 0.02	do.	E.D.
	Diacetylene	1.19 ± 0.03	do.	E.D.
	Tolan	1.19 ± 0.02	Robertson and Woodward, <i>loc. cit.</i>	X-Ray
	Diphenyldiacetylene	1.18 ± 0.03	Wiebenga, <i>loc. cit.</i>	X-Ray
	Acetylenedicarboxylic acid	1.19 ± 0.02	This series, Part II.	X-Ray
	Diacetylenedicarboxylic acid	1.185 ± 0.02	This series, Part III.	X-Ray

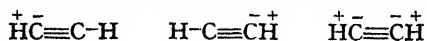
1939, **61**, 1868), who suggest an explanation on the grounds of reduced steric hindrance in the acetylene compounds. Some of the contraction may also be due to change in effective single-bond radius (Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436; Penney and Kynch, *ibid.*, p. 409). The results of Crawford and Rice (*J. Chem. Physics*, 1939, **7**, 437) and of Osborne, Garner, and Yost (*ibid.*, 1940, **2**, 131), who show that for dimethylacetylene there is little or no potential barrier to free rotation of the methyl groups, are also significant in this connection and show that double-bond character in the usual sense need not always be present when there is contraction. In view of these results it becomes easier to reconcile the non-coplanar form of the diacetylenedicarboxylic acid molecule with our bond-length measurements.

For the triple bond we obtain a value of 1.185 ± 0.02 Å. in our present investigation, and for acetylenedicarboxylic acid the value was 1.19 ± 0.02 Å. In general, the values recorded for the triple bond in carbon compounds (Table IV) are usually less than, and never greater than, the value in acetylene itself (1.204 ± 0.002 Å.). On the other hand, we might expect that in such conjugated systems the value should be slightly greater than the normal carbon-carbon triple-bond value (see also Penney and Kynch, *loc. cit.*). Although the limits of error are in all cases such that a value of 1.20 Å. is admissible, yet the fact that these values are so consistently low may be significant.

One reason for the discrepancy may be that the acetylene value of 1.204 Å. is obtained spectroscopically and may not be exactly comparable to the X-ray values (see Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436). As far as possible, however, we try to make allowances for displaced electron distributions in the X-ray work.

Another more fundamental reason for the discrepancy may be that acetylene is not a suitable standard on which to base a "normal" triple-bond length. Acetylene shows well-marked

acidic properties and the C-H link must bear considerable ionic character. Structures of the type



must play some part in this molecule and they should have the effect, by resonance energy and by electrostatic attraction, of increasing the C-H bond strength and decreasing the C-H distance. The observed value for this distance in acetylene is 1.057 Å., as against 1.093 Å. in methane, although the contraction may be partly due to an increase in the *s* character of the hybridised carbon orbitals.

In a similar way, if these structures are important, the ionic forces involved should lead to some increase in the distance between the carbon atoms. The triple-bond distance observed in acetylene may therefore represent a "stretched" rather than a "normal" triple bond.

The amount of this stretching is extremely difficult to calculate because so many different types of energy are involved. A very approximate treatment may be effected by considering only the coulombic repulsion between the two negatively charged atoms in the structure $\overset{+}{\text{H}}\text{C}\equiv\overset{+}{\text{C}}\text{H}$. It must, of course, be remembered that this structure is less important than the other two mentioned above, on account of the adjacent charges.

We consider the problem as a two-atom one and make use of the Morse function

$$V(r) = D(-2e^{-a(r-\beta)} + e^{-2a(r-\beta)})$$

For the triple bond the dissociation energy *D* is taken as 190 k.-cals. mol.⁻¹. There is considerable doubt about the value of this constant owing to the uncertain value of the heat of sublimation of diamond. The value adopted is approximately that given by Skinner (*Trans. Faraday Soc.*, 1945, **41**, 645) assuming *L* = 170; *a* is the Morse constant, $\sqrt{K/2D}$, where *K* is the force constant, taken as 15×10^5 dynes cm.⁻¹ or 2180 k.-cals. mol.⁻¹ Å.⁻²; *a* thus has the value 2.4, and β is the correct "ideal" bond length corresponding to maximum stability.

The curve for the triple bond in acetylene has an additional term due to the coulombic repulsion of the two negatively charged carbon atoms, and it may therefore be represented as

$$V = 190(-2e^{-2.4(r-\beta)} + e^{-4.8(r-\beta)}) + \frac{(\delta e)^2}{r}$$

where δ = fraction of ionic character in the bond. This function has $(\partial V/\partial r)_\beta = 0$ at $r = 1.20$ Å.

$$\text{or} \quad \left(\frac{\partial V}{\partial r}\right)_\beta = 4.8 \times 190 \{e^{-2.4(1.20-\beta)} - e^{-4.8(1.20-\beta)}\} - \frac{(\delta e)^2}{r^2} = 0$$

$$\text{or} \quad 912\{e^{-2.4(1.20-\beta)} - e^{-4.8(1.20-\beta)}\} = \frac{(\delta e)^2}{1.20^2}$$

By graphical solution of this equation for various values of δ the results in Table V were obtained. These figures show that the "ideal" triple-bond distance, β , may be somewhat shorter than the acetylene value.

TABLE V.

δ .	$(\delta e)^2/1.20^2$, k.-cal. mol. ⁻¹ .	β , Å.	δ .	$(\delta e)^2/1.20^2$, k.-cal. mol. ⁻¹ .	β , Å.
0.10	2.3	1.199	0.30	19.7	1.191
0.20	9.2	1.196	0.40	36.8	1.182

We consider, therefore, that acetylene may not be a suitable standard for the triple-bond length. One compound which might be considered to possess the "normal" triple bond is di-*tert.*-butylacetylene, the synthesis of which has recently been announced by Hennion and Banigan (*J. Amer. Chem. Soc.*, 1946, **68**, 1202). A detailed X-ray analysis of this compound would be very interesting.

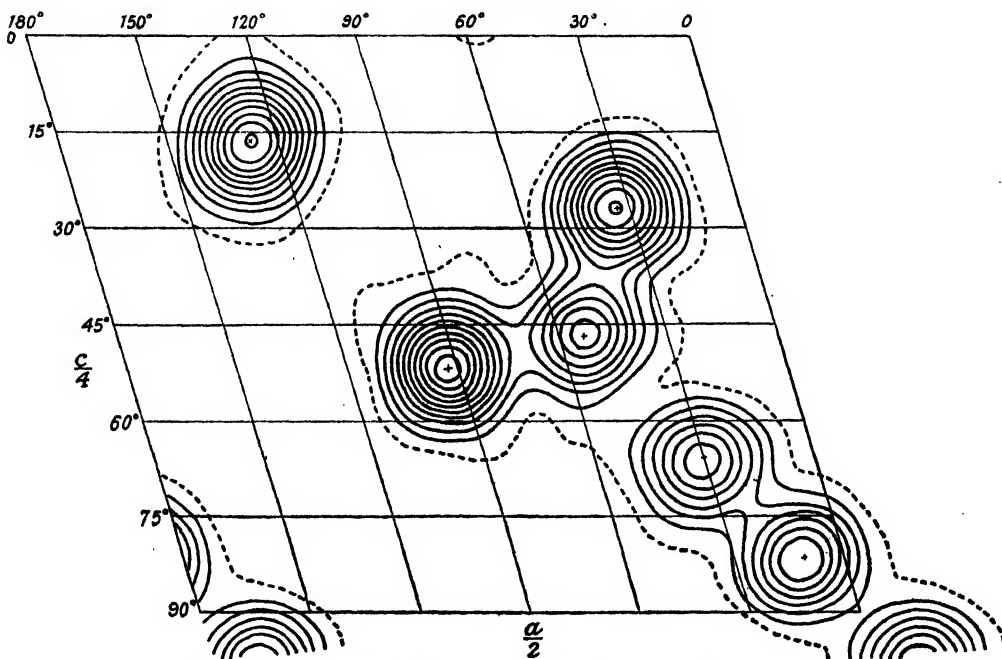
EXPERIMENTAL.

Preparation and Properties.—Diacetylenedicarboxylic acid was prepared by oxidation of the copper compound of propiolic acid with alkaline ferricyanide after Baeyer (*loc. cit.*, p. 2270). The extraction of the acid was difficult and the yields obtained were very poor, being only of the order of a few mg. from about 2 g. of propiolic acid. The compound obtained by us does not correspond to that of Baeyer, which was a monohydrate in the form of rhombic tablets, which darkened at 100°, exploded at 177°, and changed in light to a purple mass. Our product (crystallised from water or aqueous ether-light petroleum) was in the form of pale yellow monoclinic sword-like needles, elongated along the *b* axis. These crystals darkened at 95–100°, decomposed on further heating without explosion, and behaved

similarly to Baeyer's product in light. Microanalysis (Found: C, 41.4; H, 3.8. $C_6H_4O_4 \cdot H_2O$ requires C, 46.2; H, 2.6%. $C_6H_4O_4 \cdot 2H_2O$ requires C, 41.4; H, 3.5%) indicated that our compound is *diacetylenedicarboxylic acid dihydrate*. This was further confirmed by density data; the X-ray density for 4 molecules of monohydrate per unit cell is 1.28 g./c.c., or for 4 molecules of dihydrate per unit cell 1.43 g./c.c., while the observed density, determined by flotation in a mixture of ethylene bromide and benzene, is 1.43–1.45 g./c.c.

The crystals became purple on exposure to light and almost black on exposure to X-rays. With large crystals exposed to X-rays, the blackening was confined to that section of the crystal which was in the actual X-ray beam. The nature of the decomposition product was not determined, but its amount must have been very small, since quite black crystals gave X-ray photographs which showed no trace of powder rings. Prolonged exposure to X-rays did, however, produce photographs complicated by powder rings. The crystals do not lose their water of crystallisation as easily as acetylenedicarboxylic acid dihydrate, but the mosaic character of the crystals is ensured by their decomposition by light and X-rays. Copper-K α radiation was used throughout.

FIG. 5.



Co-ordinates assigned to the atoms in the asymmetric crystal unit.

Space-group Determination.—The following photographs were used to determine the unit cell and space-group. Rotation photographs about the a , b , c axes, and about $[101]$, $[111]$, $[011]$ gave the dimensions of the unit cell and showed that this was body-centred. Oscillation photographs about the b axis and moving-film photographs of the $(0kl)$, $(h0l)$, and (hkl) zones showed that the following halvings occurred: (hkl) appeared only when $(h+k+l)$ was even; $(h0l)$ appeared only when both h and l were even.

These halvings are characteristic of both the space-groups C_{2h}^4 and C_{2h}^6 , and these cannot be distinguished by X-rays since they differ only in the presence or absence of a centre of symmetry. An experiment to distinguish between these space-groups by pyroelectric effect was inconclusive. Finally, the space-group of higher symmetry C_{2h}^6 was assumed, since the calculations are considerably simplified if the structure possesses a centre of symmetry; we consider this assumption to be justified by the subsequent results.

Intensity Measurements.—Intensity estimates were carried out for the $(h0l)$ and $(0kl)$ zones. For the former the specimen employed had cross-section normal to the b axis of 0.13 mm. \times 0.31 mm., while that used for the $(0kl)$ zone had cross-section normal to the a axis of 0.29 mm. \times 0.21 mm. The intensities were estimated, and the F values derived from them, in the same way as for acetylenedicarboxylic acid dihydrate (*loc. cit.*). The range of observed intensities was about 3000 to 1.

Fourier Analysis.—The usual formulae for $\rho(x, z)$ and $\rho(y, z)$ were employed. For $\rho(xz)$ the series was summed at 900 points over the asymmetric unit, an eighth of the unit cell, the axial subdivisions being $a/60 = 0.186$ Å. and $c/120 = 0.168$ Å. Three-figure methods (Robertson, *Phil. Mag.*, 1936, **21**, 176) were used, and the positions of the contour lines were plotted on a scale of 5 cm. to 1 Å. by graphical interpolation from the arrays of summation totals. The final plot of the asymmetric unit for the b projection is shown in Fig. 5, where the final positions assigned to the atoms are indicated by small crosses.

TABLE VI.

Measured and calculated values of the structure factor.

<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	F, meas.	F, calc.	<i>hkl.</i>	$\sin \theta$ ($\lambda = 1.54$).	F, meas.	F, calc.
200	0.144	10	— 7	20,14	0.613	10	— 15
400	0.289	52	— 46	20,12	0.536	21	+ 19
600	0.433	34	— 32	20,10	0.460	54	+ 57
800	0.578	27	+ 25	208	0.384	11	+ 9
10,00	0.722	15	— 15	206	0.311	21	— 17
12,00	0.866	11	+ 9	204	0.244	120	+105
020	0.411	60	+ 82	202	0.183	108	—107
040	0.822	8	+ 9	202	0.144	39	+ 41
002	0.080	12	+ 5	204	0.182	25	+ 33
004	0.160	55	— 58	206	0.240	93	— 93
006	0.239	14	— 11	208	0.309	98	—102
008	0.319	29	— 29	20,10	0.380	16	+ 21
00,10	0.399	52	— 60	20,12	0.456	20	+ 19
00,12	0.479	23	— 20	20,14	0.534	4	— 3
00,14	0.559	25	+ 25	20,16	0.613	25	+ 28
00,16	0.638	13	+ 9	20,18	0.690	44	+ 46
00,18	0.718	10	— 7	20,20	0.768	18	— 18
00,20	0.798	13	— 7	20,22	0.847	7	— 8
00,22	0.878	14	+ 11	20,24	0.925	< 3	— 2
00,24	0.958	< 3	— 2				
				40,20	0.924	7	+ 5
011	0.210	22	— 17	40,18	0.846	4	— 4
013	0.238	32	— 35	40,16	0.772	11	— 9
015	0.287	43	— 51	40,14	0.698	8	+ 9
017	0.347	6	+ 6	40,12	0.624	13	+ 13
019	0.414	34	+ 41	40,10	0.554	11	+ 16
01,11	0.485	12	+ 12	408	0.487	48	+ 47
01,13	0.558	< 8	— 3	406	0.423	23	— 24
01,15	0.633	<10	— 2	404	0.366	18	— 9
01,17	0.709	<10	— 8	402	0.320	119	—118
01,19	0.786	8	— 9	402	0.277	16	— 13
01,21	0.863	8	+ 4	404	0.288	13	+ 11
01,23	0.941	6	+ 4	406	0.317	101	+107
				408	0.362	48	+ 52
022	0.419	24	— 21	40,10	0.419	26	— 30
024	0.442	6	+ 3	40,12	0.481	< 4	0
026	0.476	24	+ 24	40,14	0.549	28	+ 27
028	0.521	8	+ 7	40,16	0.619	41	— 32
02,10	0.573	20	— 21	40,18	0.689	8	+ 5
02,12	0.631	22	— 29	40,20	0.765	< 5	+ 2
02,14	0.694	10	— 10	40,22	0.842	< 4	— 1
02,16	0.759	< 8	+ 1	40,24	0.916	10	— 9
02,18	0.828	< 8	+ 3				
02,20	0.898	< 8	+ 1	60,18	0.936	8	+ 9
02,22	0.969	< 8	+ 9	60,16	0.866	5	+ 7
				60,14	0.796	13	— 11
031	0.618	<10	— 1	60,12	0.730	14	— 18
033	0.629	12	+ 10	60,10	0.665	9	— 11
035	0.649	<10	— 7	608	0.606	22	+ 16
037	0.677	<10	0	606	0.549	37	— 42
039	0.714	<10	+ 6	604	0.501	26	+ 27
03,11	0.757	12	— 8	602	0.461	27	+ 20
03,13	0.806	<10	— 4	602	0.417	< 5	— 1
03,15	0.860	10	+ 6	604	0.422	48	+ 40
03,17	0.917	< 8	+ 1	606	0.430	39	+ 34
03,19	0.978	< 6	— 4	608	0.458	23	+ 22
				60,10	0.498	10	+ 7
042	0.827	< 8	+ 1	60,12	0.544	40	— 42
044	0.838	< 8	+ 5	60,14	0.599	17	— 17
046	0.857	< 8	— 1	60,16	0.660	30	— 31
048	0.882	< 8	— 4	60,18	0.724	9	+ 9
04,10	0.914	< 8	— 1	60,20	0.791	< 5	+ 3
04,12	0.952	< 6	— 4	60,22	0.860	5	+ 6
				60,24	0.930	10	+ 9
20,22	0.925	5	+ 4	80,16	0.972	< 3	— 2
20,20	0.847	8	— 9	80,14	0.908	< 4	+ 1
20,18	0.769	15	— 14	80,12	0.845	< 5	0
20,16	0.691	15	— 17	80,10	0.786	30	— 32

TABLE VI.—continued.

Measured and calculated values of the structure factor.

sin θ ($\lambda = 1.54$).				sin θ ($\lambda = 1.54$).			
<i>hkl</i> .	$\sin \theta$	F, meas.	F, calc.	<i>hkl</i> .	$\sin \theta$	F, meas.	F, calc.
808	0.734	13	+ 12	10,04	0.691	< 5	+ 5
806	0.684	29	+ 24	10,06	0.689	13	- 13
804	0.640	10	+ 13	10,08	0.696	29	- 29
802	0.605	12	+ 14	10,010	0.715	39	+ 37
802	0.559	12	- 5	10,012	0.741	23	+ 18
804	0.551	56	- 50	10,014	0.775	5	+ 5
806	0.556	28	- 28	10,016	0.815	< 5	+ 1
808	0.574	10	+ 8	10,018	0.857	< 5	- 1
80,10	0.599	22	+ 17	10,020	0.909	3	- 4
80,12	0.634	28	- 26	10,022	0.961	8	- 8
80,14	0.678	23	+ 23				
80,16	0.727	< 5	0	12,06	0.961	< 3	- 3
80,18	0.781	4	- 5	12,04	0.923	7	- 8
80,20	0.839	7	+ 7	12,02	0.891	< 4	- 4
80,22	0.902	< 4	+ 2	12,02	0.845	8	+ 7
80,24	0.966	< 3	+ 2	12,04	0.834	< 5	- 1
				12,06	0.828	21	+ 15
10,0,12	0.969	< 3	+ 8	12,08	0.831	3	- 4
10,0,10	0.914	< 4	+ 3	12,010	0.841	6	- 5
10,08	0.865	5	- 3	12,012	0.860	5	- 4
10,06	0.819	5	- 7	12,014	0.885	6	+ 5
10,04	0.779	6	+ 6	12,016	0.916	3	+ 1
10,02	0.746	6	+ 8	12,018	0.953	9	- 8
10,02	0.700	10	- 9				

The y co-ordinates together with a check on the z co-ordinates were obtained from the projection along the a axis shown in Fig. 2. $\rho(yz)$ was summed at 225 points over the asymmetric unit, the axial subdivisions being $b/30 = 0.125$ Å. and $(c \sin \beta)/60 = 0.322$ Å. The summations were carried out, and the contour map drawn, as described above for the b projection. Considerable overlapping occurs in the a axis projection and the y co-ordinates are not fixed as rigorously as we should like, but no better resolution can be obtained by two-dimensional methods and any ambiguity can be resolved only by means of three-dimensional Fourier synthesis.

From the final co-ordinates (Table I), all the structure factors were recalculated and the results are given in Table VI. For this calculation the structure factor F has been expressed in the form $fS = F$. For f we have used a composite empirical atomic scattering factor which gives better results than that used in the case of acetylenedicarboxylic acid dihydrate and oxalic acid dihydrate (*q.v.*). The f values used are as follows:

sin θ ($\lambda = 1.54$)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
f	334	282	224	167	113	80	54	34	19	13

The maximum value of f , at sin $\theta = 0$, may be taken as $F(000) = 360$, the total number of electrons in the unit cell.

S is the geometric structure factor. It is conveniently put into the form

$$60 S = \Sigma 8A \cos 2\pi \left(\frac{hx}{a} + \frac{lz}{c} \right) \cos 2\pi \frac{hy}{b}, \text{ when } l \text{ is even}$$

$$60 S = \Sigma - 8A \sin 2\pi \left(\frac{hx}{a} + \frac{lz}{c} \right) \sin 2\pi \frac{hy}{b}, \text{ when } l \text{ is odd}$$

The carbon and oxygen coefficients are weighted in the ratio of 6 to 9, so that for a carbon atom $A = 1$ and for an oxygen atom $A = 1.5$. Since there are six atoms in the asymmetric unit, three of which have $A = 1$ and three $A = 1.5$, the maximum value of S is conveniently taken as unity.

The percentage discrepancy finally obtained, expressed as

$$\frac{\Sigma (|F \text{ meas.}| - |F \text{ calc.}|)}{\Sigma |F \text{ meas.}|} \times 100$$

is 11.0 for the ($h0l$) reflections, 14.8 for the ($0kl$) reflections, and 11.9 for all reflections.

In the b axis projection (Fig. 1) the F values for the (802) and (10, 0, 8) planes were omitted from the Fourier summation owing to uncertainty of sign.

We thank Dr. E. Warhurst for much helpful discussion during the progress of this work, and one of us (J. D. D.) is indebted to the Carnegie Trustees for a Scholarship.

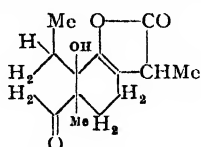
216. The Constitution of ψ -Santonin. Part IV. A Study of the Butenolide System.

By WESLEY COCKER and STANLEY HORNSBY.

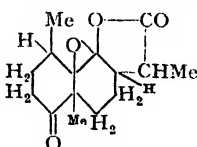
The speeds of bromination and hydrogenation, and the products of the latter, of ψ -santonin and a number of $\alpha\beta$ - and $\beta\gamma$ -butenolides have been compared. Spectroscopic observations have also been made. Possible structures for ψ -santonin are discussed.

Experiments with dihydro- ψ -santonin suggest that this compound can be represented as (III).

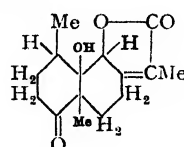
In Part I of this series Clemo and Cocker (*J.*, 1946, 30) discussed the chemistry of ψ -santonin and suggested that one of the structures (Ia) and (II) represented the constitution of this compound, but it was not then possible to decide which was the more likely.



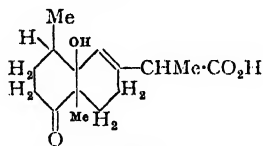
(Ia.)



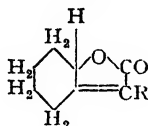
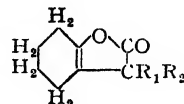
(Ib.)



(II.)



(III.)

(IV; R = H;
V; R = Me.)

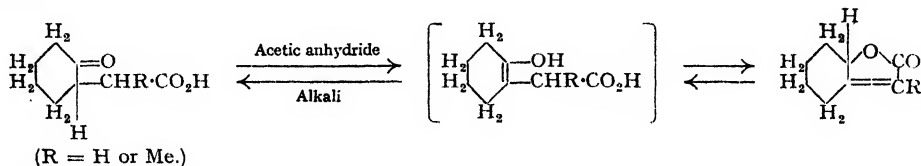
(VI.)

Colour reactions with sodium nitroprusside (cf. Jacobs and Hoffmann, *J. Biol. Chem.*, 1925, 67, 333; Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, 6, 273) strongly suggested the presence of a $\beta\gamma$ -butenolide, whilst the slow reduction of ammoniacal nitrate suggested an $\alpha\beta$ -butenolide (cf. Jacobs, Hoffmann, and Gustus, *J. Biol. Chem.*, 1926, 70, 1).

In view of these opposing reactions it was felt desirable to study the properties of a number of butenolides of both the $\alpha\beta$ - and the $\beta\gamma$ -type in which, as in ψ -santonin, the butenolide is fused in the $\beta\gamma$ -position to a cyclohexane ring.

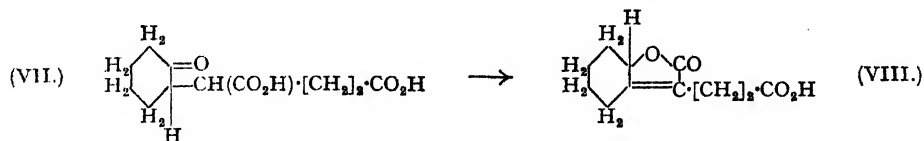
Although various α - and β -substituted butenolides have been studied in which the substituent was cyclohexyl (Elderfield *et al.*, *J. Org. Chem.*, 1941, 6, 289) and a few of the above mentioned fused lactones have been prepared, no systematic study of the properties of the latter compounds seems to have been undertaken. We have therefore prepared and studied the properties of the lactones of the following acids, namely, 2-hydroxycyclohexylideneacetic acid (IV), 2-hydroxycyclohexylidene- α -propionic acid (V), and 2-hydroxycyclohex-1-enyl- α -isobutyric acid (VI; R₁ = R₂ = Me).

The $\alpha\beta$ -butenolides (IV and V) were prepared by the cyclisation of 2-ketocyclohexylmalonic or 2-ketocyclohexyl- α -propionic acid with acetic anhydride; the reactions are apparently as follows:



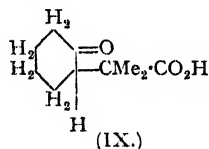
That the product of the cyclisation is an $\alpha\beta$ -butenolide is shown by the fact that when the lactone obtained from 2-ketocyclohexylmalonic acid was submitted to ozonolysis in chloroform, 2-ketocyclohexanol was obtained. Although neither glyoxylic nor oxalic acid was obtained in this reaction, yet when the same lactone was oxidised with neutral permanganate a mixture was obtained from which, in addition to some unchanged lactone, an unidentified carbonyl compound, adipic acid, and oxalic acid were isolated. We do not consider that the isolation of adipic acid and oxalic acid is necessarily of diagnostic value, but together with the evidence from the

ozonolysis experiments there is adequate proof of the $\alpha\beta$ -butenolide structure. The lactone from 2-ketocyclohexyl- α -propionic acid also gave 2-ketocyclohexanol on ozonolysis. Furthermore, Kendal and Osterberg (*J. Amer. Chem. Soc.*, 1927, 49, 2047) showed conclusively by ozonolysis experiments on the product that when 2-ketocyclohexyl- α -glutaric acid (VII) is cyclised it yields the $\alpha\beta$ -butenolide (VIII), a result which is analogous to those we obtained.

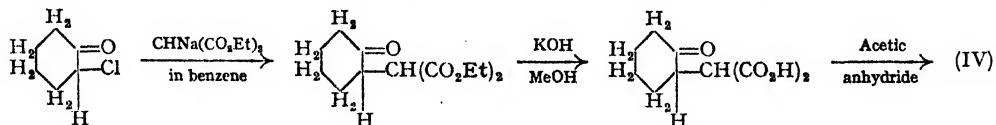


Other workers, e.g., Grewe (*Ber.*, 1939, 72, 426), have concluded that when γ -keto-acids of the type already mentioned are cyclised the result is a $\beta\gamma$ -lactone. This worker assumed that the product of cyclisation of 2-ketocyclohexyl- α -benzylacetic acid was (VI; $R_1 = \text{H}$; $R_2 = \text{CH}_2\text{Ph}$). He found, however, that on catalytic hydrogenation the butenolide system was unaffected, whereas the aromatic nucleus suffered reduction. This resistance to hydrogenation was similar to that shown by lactone (V), and we believe that Grewe's lactone was actually of the $\alpha\beta$ -butenolide type.

The production of an $\alpha\beta$ -butenolide in the manner stated does not appear to be in accordance with the work of Kon and Speight (*J.*, 1926, 2727) who showed that, presumably as a result of the tendency of the six membered ring to acquire a double bond, the equilibrium between cyclohex-1-enylacetic acid and its esters and cyclohexylideneacetic acid and its esters lies on the side of the former compounds. By analogy we should have expected the equilibrium between the $\beta\gamma$ - and $\alpha\beta$ -butenolides under discussion to lie on the side of the former, but it appears that in these lactones the tendency of the double bond to conjugate with the carbonyl group predominates. It was obvious, therefore, that a $\beta\gamma$ -butenolide of type (VI) could only be prepared if the tautomeric system were blocked, i.e., if R_1 and R_2 were groups other than H. We therefore prepared and cyclised 2-ketocyclohexyl- α -isobutyric acid (IX) which yielded the required lactone (VI; $R_1 = R_2 = \text{Me}$).



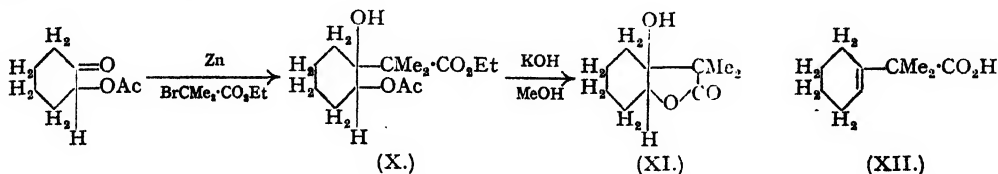
The lactone of 2-hydroxycyclohexylideneacetic acid (IV) was prepared by McCrae, Charlesworth, and Alexander (*Canadian J. Res.*, 1943, 21B, 1) who oxidised the lactone of 2-hydroxycyclohexylacetic acid (Coffey, *Rec. Trav. chim.*, 1923, 42, 382) with bromine and magnesium hydroxide. The keto-acid so obtained was then cyclised by heating at 200° in a vacuum, and the butenolide was obtained as a solid, m. p. 7—8°. We preferred to use a more economical method for the preparation of this lactone. 2-Chlorocyclohexanone was condensed with ethyl sodiomalonate and the ester obtained was saponified with methyl-alcoholic potash to give 2-ketocyclohexylmalonic acid, which was simultaneously lactonised and decarboxylated by refluxing with an excess of acetic anhydride.



By this method we obtained the butenolide as a crystalline solid, m. p. 29—30°. Lactone (V) was prepared in a similar manner, and we found this to be preferable to the method of Clemo and Cocker (*loc. cit.*) who started from 2-carbethoxycyclohexanone and ethyl α -bromopropionate.

The preparation of the lactone of 2-hydroxycyclohex-1-enyl- α -isobutyric acid was troublesome and a number of routes were tried before a satisfactory one was found. The first was by the condensation of 2-carbethoxycyclohexanone in presence of sodium with ethyl α -bromoisobutyrate, and the product, which gave only poor analysis results, was hydrolysed with 8% methyl-alcoholic potash. Unfortunately this gave only pimelic acid and a hygroscopic acid which gave no carbonyl reactions. In the second method 2-acetoxycyclohexanone was condensed in presence of zinc with ethyl α -bromoisobutyrate to give ethyl 1-hydroxy-2-acetoxycyclohexyl- α -isobutyrate (X) in fair yield. All attempts to dehydrate this ester failed. It was boiled with acetic anhydride, with and without anhydrous sodium acetate; it was heated at 160° with potassium hydrogen sulphate; and finally it was heated under reflux with pyridine and phosphoryl chloride: all these treatments left it unchanged. Torrey, Kuck, and Elderfield

(*J. Org. Chem.*, 1941, 6, 289) found similar difficulty in the dehydration of certain tertiary alcohols, but all their compounds yielded to the dehydrating action of a boiling mixture of pyridine and phosphoryl chloride.



When the ester (X) was hydrolysed with alcoholic potash and the mixture acidified, a lactone $\text{C}_{10}\text{H}_{16}\text{O}_3$ was obtained which presumably was (XI). Attempts to dehydrate this lactone were again unsuccessful, but it was found that on heating it with 30% alcoholic sulphuric acid a very small yield of a carbonyl compound was obtained, and this gave a 2 : 4-dinitrophenyl-hydrazone which proved to be identical with that obtained from 2-ketocyclohexyl- α -isobutyric acid. The ketone was probably produced from (XI) by a pinacol-pinacolone rearrangement. The method was, however, of little preparative value.

Finally the required lactone (VI; $\text{R}_1 = \text{R}_2 = \text{Me}$) was obtained by a method similar to that used by McCrae, Charlesworth, and Alexander (*loc. cit.*) for the preparation of (IV). Ethyl 1-hydroxycyclohexyl- α -isobutyrate (Wallach and Mallinson, *Annalen*, 1908, 360, 68) was obtained by the condensation of cyclohexanone with ethyl α -bromoisobutyrate in presence of zinc, and it was dehydrated and then saponified to yield cyclohex-1-enyl- α -isobutyric acid. Von Braun and Münch (*Annalen*, 1928, 465, 55) effected the lactonisation of this acid with hydrogen bromide in acetic acid. We performed the lactonisation with 50% sulphuric acid, and the product was oxidised to 2-ketocyclohexyl- α -isobutyric acid. The lactonisation of cyclohex-1-enyl- α -isobutyric acid mentioned above was, however, accompanied by the production of 1-isopropylcyclohexene. Wallach and Mallinson (*loc. cit.*) showed that this compound could be obtained from isopropylidenecyclohexane by heating with sulphuric acid. Lactone (VI; $\text{R}_1 = \text{R}_2 = \text{Me}$) was finally obtained by the cyclisation of 2-ketocyclohexyl- α -isobutyric acid with acetic anhydride.

Various attempts were made to prepare the lactone of 1-hydroxy-3 : 4-dihydronaphthalene-2-isobutyric acid, but these were unsuccessful.

Hydrogenation Experiments.— ψ -Santonin and the lactones (IV), (V), and (VI; $\text{R}_1 = \text{R}_2 = \text{Me}$) were separately submitted to catalytic hydrogenation at 1 atmosphere pressure of hydrogen, at room temperature using (a) palladised charcoal and (b) Adams's platinum oxide catalyst. The results of these experiments are shown in Fig. 1 and Table I. It can readily be seen that, of all the lactones employed, only ψ -santonin was hydrogenated with any rapidity when palladised charcoal was employed, and here absorption ceased when one molecule of hydrogen had been taken up. The product of the reaction was dihydro- ψ -santonin (III), an unsaturated carboxylic acid. With the same catalyst the $\alpha\beta$ -butenolide (IV) absorbed one molecule of hydrogen in about 16 hours and the product was the saturated lactone of 2-hydroxycyclohexylacetic acid. On the other hand the $\alpha\beta$ -butenolide (V), in which the $\alpha\beta$ -double bond is further protected, absorbed about 0.1 molecule of hydrogen in fifteen minutes in presence of palladised charcoal after which no further absorption took place. The addition of Adams's catalyst at this stage effected no further absorption apart from that expected in the reduction of the catalyst. On working up the reaction mixture only (V) was isolated. The $\beta\gamma$ -butenolide (VI; $\text{R}_1 = \text{R}_2 = \text{Me}$) was unaffected by hydrogen and palladised charcoal, but in presence of Adams's catalyst absorption took place at a very rapid rate and 2 molecules of hydrogen were taken up in 15 minutes with the production of cyclohexyl- α -isobutyric acid, identical with the acid obtained from the hydrogenation of cyclohex-1-enyl- α -isobutyric acid (XII) in presence of Adams's catalyst. In presence of the same catalyst ψ -santonin absorbed one molecule of hydrogen at a speed very similar to that of (VI), but further hydrogenation was slower and was complicated by the reduction of the keto-group. Under similar conditions (IV) was reduced rapidly, but not so rapidly as either ψ -santonin or (VI), and again a saturated lactone was obtained. Finally we found that cyclohex-1-enyl- α -isobutyric acid (XII) was unaffected by hydrogen and palladised charcoal, which falls into line with the absence of reactivity of dihydro- ψ -santonin (III) towards the same reagents, and it is of interest to record that Thakur (*J.*, 1933, 1481) found that cyclohex-1-enyl- α -propionic acid was only slowly reduced with Adams's catalyst.

These results clearly indicate that ψ -santonin and the $\beta\gamma$ -lactone behave alike in the

production of a deoxy-acid on hydrogenation; a result which is similar to that found by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601) in the investigation of a number of simple $\beta\gamma$ -butenolides. These workers and Paist, Blout, Uhle, and Elderfield (*loc. cit.*) also found that simple $\alpha\beta$ -butenolides are reduced to the corresponding saturated lactones. Both ψ -santonin and (VI; $R_1 = R_2 = \text{Me}$) are more rapidly hydrogenated than the $\alpha\beta$ -butenolides (IV) and (V), but it is well known that $\alpha\beta$ -double bonds, and particularly protected $\alpha\beta$ -double bonds, are very often sluggish or resistant to hydrogenation (Haworth, *Ann. Reports*, 1937, **34**, 328).

FIG. 1.

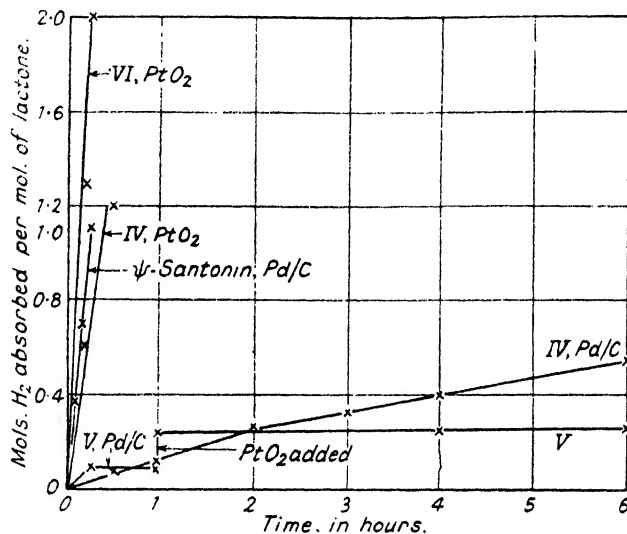
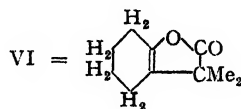
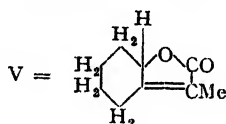
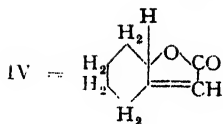
Hydrogenation of ψ -santonin and the synthetic lactones.

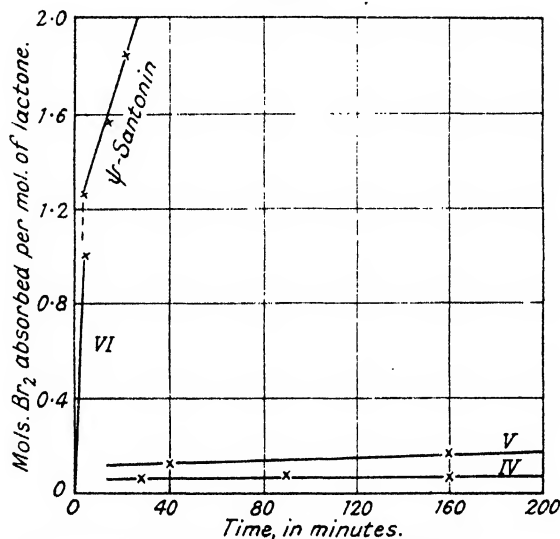
TABLE I.

Hydrogenation Experiments on the Lactones at 1 atm./18° ± 3°.

Lactone.	Catalyst.	Time for uptake of hydrogen.		Product.
		1 mol.	2 mols.	
ψ -Santonin	$\left\{ \begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array} \right.$	15 minutes 10 "		$\left. \vphantom{\begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array}} \right\}$ Dihydro ψ -santonin (III)
	$\left\{ \begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array} \right.$	No absorption	15 minutes	
	$\left\{ \begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array} \right.$	16 hours 30 minutes		$\left. \vphantom{\begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array}} \right\}$
	$\left\{ \begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array} \right.$	0.1 mol. in 15 mins. No further absorption		$\left. \vphantom{\begin{array}{l} \text{Pd/C} \\ \text{PtO}_2, \text{H}_2\text{O} \end{array}} \right\}$

Halogenation Experiments. (With C. LIPMAN.)—It is well known that $\alpha\beta$ -unsaturated acids and esters absorb bromine less rapidly than their $\beta\gamma$ -isomerides (Sudborough and Thomas, *J.*, 1910, 97, 715, 2450) and this method was used by Linstead (*J.*, 1927, 355) for determination of the position of equilibrium in mixtures of isomeric unsaturated acids. By a method similar to that advocated by Linstead we have studied the comparative speeds of bromination of ψ -santonin and the three other lactones. For this purpose equivalent quantities (1/1200 g.-mol.) of the lactones in $N/60$ -solution in carbon tetrachloride, containing 30% acetic acid necessary to obtain solution, were treated with 2 mols. of $N/15$ -solution of bromine in carbon tetrachloride, the final concentration of the bromine in the mixture being $N/30$, and the carefully stoppered vessels were placed in a dark container at 16–17°. Aliquot portions of the solutions were withdrawn at intervals and after treatment with potassium iodide the liberated iodine was titrated with $N/40$ -thiosulphate. 2 Mols. of bromine were employed because ψ -santonin brominates first to give a monobromo-compound by substitution and then one molecule of bromine adds to give a tribromo-compound (Clemo and Cocker, *loc. cit.*). Fig. 2 and Table II

FIG. 2.



Bromination of ψ -santonin and the synthetic lactones.
(IV, V, and VI as for Fig. 1.)

TABLE II.

Lactone	Bromine absorption in mols. in x minutes.										
	$x = 5$	10	15	20	30	40	90	160	320	420	900
ψ -Santonin	1.242	—	1.54	1.82	1.99	—	—	—	—	—	—
(VI)	1.11	1.06	—	—	—	—	—	—	—	—	—
(IV)	—	—	—	—	0.04	—	0.06	0.05	—	—	0.15
(V)	—	—	0.11	—	—	0.14	—	0.17	0.19	0.21	—

(IV, V, and VI as for Fig. 1.)

show that ψ -santonin and the $\beta\gamma$ -butenolide (VI; $R_1 = R_2 = \text{Me}$) absorb bromine at approximately the same rate, although it should be remembered that it is the upper part of the graph of ψ -santonin which must be compared with that of (VI), since the lower part of the ψ -santonin graph, which lies upon that of (VI), represents the substitution reaction. When monobromo- ψ -santonin was brominated using one molecule of bromine its rate of bromination was similar to that found for the absorption of the second molecule of bromine in ψ -santonin itself, so that the influence of the hydrogen bromide produced in the substitution reaction in ψ -santonin need not be considered. When (VI) was brominated with 1 mol. of bromine there was no change in the rate of reaction. The absorption of bromine by the $\alpha\beta$ -butenolides (IV and V) is very slow, but the initial rapid absorption is interesting and is paralleled by a similar absorption in the hydrogenation of (V). This is probably due to the presence of some $\beta\gamma$ -butenolide in (IV) and (V).

Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1946, 68, 2332) used Hanus solution (IBr) as a reagent for differentiating between $\alpha\beta$ - and $\beta\gamma$ -lactones. They found that the latter reacted much more rapidly than the former with this reagent.

The bromination and hydrogenation results seem to be evidence in favour of the adoption of structure (Ia) for ψ -santonin.

Spectroscopic Evidence.—Spectroscopic studies do not appear to support the $\beta\gamma$ -structure, and in fact, neglecting the absorption due to the carbonyl group, there is a striking resemblance between the absorptions of ψ -santonin and the $\alpha\beta$ -lactone (V). In each case there is high intensity absorption at the extreme end of the usual ultra-violet range, and in neither is a maximum discernible. This is similar to the experience noted by other workers such as Haynes and Jones (*J.*, 1946, 954) and Ruzicka *et al.* (*Helv. Chim. Acta*, 1942, 25, 435; 1944, 27, 186) with a number of simple $\alpha\beta$ -unsaturated lactones. The $\beta\gamma$ -lactone (VI) absorbs with a much smaller intensity than either ψ -santonin or lactone (V) at comparable wave-lengths.

TABLE III.
Light-absorption Data for Unsaturated Lactones.

	λ , A.	ϵ .	
ψ -Santonin ...	2900 *	35	* Maximum characteristic of the isolated $>C=O$ group.
(V)	2000 †	14,000	† Maximum not discernible.
(V)	2200 †	12,000	
(VI)	2200 †	3,851	

Colour Reactions and Reactions with Tollens's Reagent.—Lactones (IV) and (V) both instantaneously reduced Tollens's reagent whilst ψ -santonin and (VI; $R_1 = R_2 = \text{Me}$) gave a silver mirror only after twelve hours. These reactions were carried out as follows. A solution of 10 mg. of lactone in 1 c.c. of purified pyridine was treated with 1 c.c. of Tollens's reagent, prepared from equal volumes of 10% sodium hydroxide and 10% silver nitrate to which 10% ammonia was added dropwise until the precipitated silver oxide had disappeared.

The results are interesting since they appear to show that ψ -santonin and lactone (VI; $R_1 = R_2 = \text{Me}$) are alike in the position of the double bond (*i.e.*, they are $\beta\gamma$ -butenolides), but the slowness of reduction of the reagent by these butenolides is contrary to the experience of Jacobs, Hoffmann, and Gustus (*loc. cit.*) who found that the $\beta\gamma$ -butenolides they investigated gave immediate reduction of Tollens's reagent, whereas the $\alpha\beta$ -butenolides were very sluggish. It must be remembered, however, that Jacobs and his co-workers were not investigating lactones fused to a cyclohexane ring, and it is more than likely that this is the explanation of the differing results.

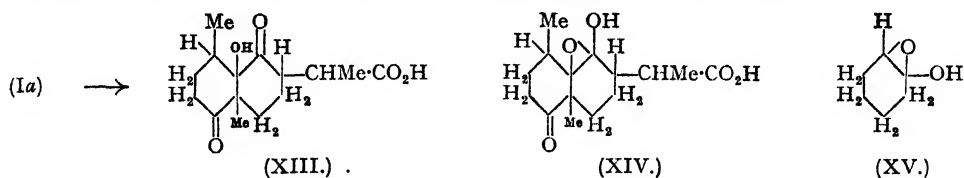
The Legal tests when applied to all the synthetic lactones in the manner recommended by Paist, Blout, Uhle, and Elderfield (*loc. cit.*) were most unsatisfactory. There was little change in colouration with sodium nitroprusside until the solution became distinctly alkaline to phenolphthalein and it is felt that as applied to these particular lactones the Legal test has little diagnostic value.

Cardiac Activity of the Lactones.—The effect on the isolated frog heart of ψ -santonin, the lactones (IV), (V), (VI), and the lactone of 2-hydroxycyclohexylacetic acid was tried through the courtesy of the late Dr. J. Secker of the Department of Physiology of King's College. The concentration of lactone used was 1 mg. per c.c. of 10% aqueous alcohol and it was found that 1 drop of solution of all the butenolides produced cardiac inhibition, whilst the saturated lactone was ineffective. It appears, therefore, that the unsaturated lactone system has some cardiac effect, but it is not specific for either the $\alpha\beta$ - or the $\beta\gamma$ -type. No experiments were performed on cats but it is highly unlikely that any of the lactones would have important effects (*cf.* Swain, Todd, and Waring, *J.*, 1944, 548).

If the $\beta\gamma$ -butenolide structure (I) for ψ -santonin is adopted there are certain experimental results which require an explanation. In the first place when ψ -santonin is saponified with methyl-alcoholic potash a solution is obtained from which the starting material is regenerated even on acidification at 0°. Many experiments were performed but in none of these was there any evidence for the production of a diketo-acid on saponification of ψ -santonin, whereas the diketo-acid (XIII) would be expected from structure (Ia). All the synthetic butenolides give keto-acids on saponification. One possible explanation could be that on hydrolysis the keto-acid undergoes isomeric change with the formation of the cyclic alcohol (XIV), in the same way that Bergmann and Gierth (*Annalen*, 1926, 448, 48) found that 2-ketocyclohexanol can exist in

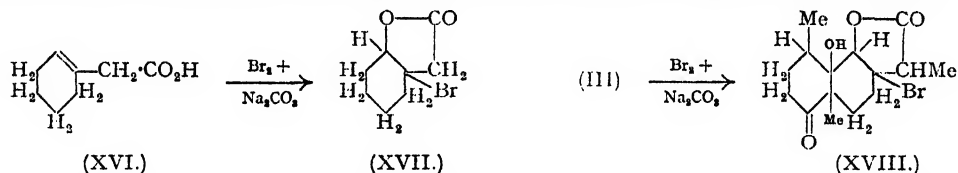
the oxido-form (XV). It is possible that on acidification $^-(XIV)^-$ could lactonise and undergo isomeric change with the formation of (Ia).

A further difficulty in the way of acceptance of structure (Ia) lies in the fact that it has been shown that in the butenolides fused to the cyclohexane ring, unless tautomeric change is



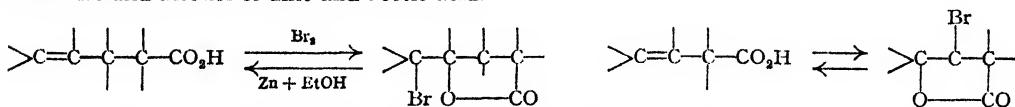
impossible as in (VI), the double bond is found in the $\alpha\beta$ -position. Why then should ψ -santonin be a $\beta\gamma$ -butenolide? We believe that the hydroxyl group is somehow connected with this problem and it may be that structure (Ib) is more acceptable than (Ia), but until we have succeeded in synthesising certain hydroxylated butenolides it would be well to withhold further comment.

Some Experiments with Dihydro- ψ -santonin.—This compound readily decolourises bromine water, and in quantitative experiments performed under identical conditions with those already described it was found that one mol. of bromine was completely absorbed per mol. of acid in less than 5 minutes. This result is strongly suggestive of a $\beta\gamma$ -unsaturated acid. Moreover such $\beta\gamma$ -acids readily form bromo-lactones on treatment, in sodium carbonate, with bromine water. Thus Harding, Haworth, and Perkin (*J.*, 1908, 95, 1963) obtained a bromo-lactone, to which they assigned the structure (XVII), when cyclohex-1-enylacetic acid (XVI) was brominated in sodium carbonate. In a similar manner when dihydro- ψ -santonin was treated in sodium carbonate with bromine water a white crystalline solid was obtained. This was a bromo-lactone, $C_{15}H_{21}O_4Br$, and to this compound by analogy we assign structure (XVIII).



The possibility that the bromo-lactone is a β -lactone may be ruled out, since we have shown already that the $\alpha\beta$ -double bond is resistant to attack of bromine and the mechanism of addition of hypobromous acid is undoubtedly similar to that of bromine itself.

Such bromo-lactones as those mentioned above should be capable of reduction to the corresponding unsaturated acids. Thus Winterstein and his co-workers (*Z. physiol. Chem.*, 1931, 199, 25, 37, 46, 56, 64, 75) have shown that $\beta\gamma$ - and $\gamma\delta$ -unsaturated acids can be converted into crystalline bromo-lactones from which the unsaturated acids are regenerated by reduction with zinc and alcohol or zinc and acetic acid.



When the bromo-lactone (XVIII) was refluxed with zinc dust in alcohol it was smoothly reconverted into dihydro- ψ -santonin. In an analogous manner cyclohex-1-enyl- α -isobutyric acid was converted into a bromo-lactone, $C_{10}H_{15}O_2Br$, from which the unsaturated acid was again obtained by reduction with zinc and alcohol.

We consider that the above evidence strongly supports the structure (III) suggested for dihydro- ψ -santonin.

EXPERIMENTAL.

Lactone of 2-Hydroxycyclohexylideneacetic Acid (IV). 2-Ketocyclohexylmalonic Acid.—Ethyl malonate (63.4 g.) was added dropwise to a stirred and boiling suspension of powdered sodium (9.1 g.) in benzene (300 c.c.) and the reaction was continued until all the sodium had disappeared. The cooled mixture was then slowly treated, with stirring, with 2-chlorocyclohexanone (63 g.). After 1 hour in the cold the mixture was heated on the water-bath and refluxed, with stirring, for 8 hours. It was then cooled and acidified with dilute acetic acid, and the benzene layer was separated, washed with water, and dried. On distillation ethyl 2-ketocyclohexylmalonate (49 g.) was collected as a colourless oil, b. p. 150–151°/3 mm. (Found: C, 61.5; H, 7.9. $C_{15}H_{20}O_5$ requires C, 60.9; H, 7.8%). This ester was

hydrolysed by heating for 2 hours under reflux with a solution of potassium hydroxide (34 g.) in methyl alcohol (500 c.c.) and water (50 c.c.). Methyl alcohol was then removed and the residue was diluted with water, shaken with charcoal, and filtered. The filtrate was acidified, saturated with ammonium sulphate, and extracted several times with ethyl acetate from which the required 2-ketocyclohexylmalonic acid was obtained (19 g.), m. p. 160°. It crystallised from water as colourless needles, m. p. 168–169° (decomp.). McCrae, Charlesworth, and Alexander (*loc. cit.*) give m. p. 163° (Found: C, 54.1; H, 6.0; equiv., 105.1. Calc. for $C_8H_{12}O_5$: C, 54.0; H, 6.0%; equiv., 100). Its 2:4-dinitrophenylhydrazones crystallised from alcohol as yellow needles, m. p. 218–219° (decomp.) (Found: C, 48.0; H, 4.5. $C_{18}H_{18}O_8N_4$ requires C, 47.4; H, 4.2%).

The above acid (19 g.) was gently refluxed for 2 hours with acetic anhydride (80 g.) and the acetic anhydride was then removed under reduced pressure. The residual oil was dissolved in ether, washed several times with sodium hydrogen carbonate solution, dried, and distilled. The product distilled almost completely at 131–133°/3–4 mm. and on cooling it solidified to a mass of colourless needles of (IV), m. p. 29–30° (Found: C, 69.3; H, 7.3. Calc. for $C_8H_{10}O_4$: C, 69.6; H, 7.25%). On hydrolysis with 10% methyl-alcoholic potash the lactone yielded 2-ketocyclohexylacetic acid, m. p. 73°, undepressed by admixture with an authentic specimen prepared by heating 2-ketocyclohexylmalonic acid (cf. McCrae *et al.*, *loc. cit.*) (Found: equiv., 150. Calc. for $C_8H_{12}O_3$: equiv., 156). 2-Ketocyclohexylacetic acid 2:4-dinitrophenylhydrazones crystallised from dilute alcohol as yellow needles, m. p. 193–194° (Found: C, 50.5; H, 4.8. $C_{18}H_{18}O_8N_4$ requires C, 50.0; H, 4.8%).

Oxidation of the Lactone.—(a) *With neutral potassium permanganate.* The lactone (1.0 g.) in water (10 c.c.) containing magnesium sulphate (3 g.) was slowly treated, with shaking, with 1% permanganate (75 c.c.). The mixture was then further shaken for 30 minutes. It was made alkaline to phenolphthalein and filtered. The filtrate was warmed for 30 minutes on the water-bath and extracted with ether from which unoxidised lactone, m. p. 29–30°, was obtained. The alkaline residue was evaporated to a very small bulk, acidified with sulphuric acid, and extracted many times with ether from which adipic acid (crude, m. p. 140°) was isolated. The aqueous residue was freed from sulphate ions, buffered with sodium acetate, and treated with calcium chloride; calcium oxalate was produced, soluble in hydrochloric acid and capable of reducing acid potassium permanganate.

(b) *With ozone.* The lactone (0.5 g.) in purified chloroform (25 c.c.) was subjected to ozonised oxygen (0.009 g.-mol. O_3 /hr.) for 30 minutes. The solvent was then removed in a vacuum at room temperature and the residue was shaken thoroughly with water and left overnight. The solution was treated with sodium carbonate (0.5 g.) and steam distilled. The distillate yielded a 2:4-dinitrophenylhydrazones which on crystallisation from alcohol gave m. p. 231–232° undepressed by an authentic specimen of the 2:4-dinitrophenylhydrazones of 2-ketocyclohexanol. Neither glyoxylic acid nor oxalic acid was, however, identified in the residue from the steam distillation.

Hydrogenation.—The above lactone (1.0002 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0.5 g.) absorbed 166.4 c.c. of hydrogen at 15.5°/761 mm. This is equivalent to 0.98 mols. of hydrogen per mol. of lactone. The reaction was complete in 16 hours. The glacial acetic acid was removed under reduced pressure and the residue was distilled to give the lactone of 2-hydroxycyclohexylacetic acid (0.9 g.), b. p. 110–111°/3–4 mm. (Found: C, 68.3; H, 8.6. Calc. for $C_8H_{12}O_3$: C, 68.6; H, 8.6%). Its phenylhydrazide crystallised from dilute acetic acid in colourless plates, m. p. 168° (Found: C, 67.7; H, 8.2. $C_{14}H_{18}O_3N_2$ requires C, 67.7; H, 8.1%). No acid products were isolated from the reduction, and when the reduced lactone was hydrolysed by alkali and the solution acidified it was regenerated unchanged.

When (IV) (0.3070 g.) was hydrogenated in acetic acid (20 c.c.) containing Adams's platinum oxide catalyst (0.05 g.) at 20°/769 mm. hydrogen was rapidly absorbed and absorption was complete (1.17 mols. of hydrogen per mol. lactone) in 30 minutes. When the acetic acid was removed the residue was found to be insoluble in sodium carbonate, and it gave a phenylhydrazide identical with that described above.

Lactone of 2-Hydroxycyclohexylidene- α -propionic Acid (V). 2-Ketocyclohexyl- α -propionic Acid.—The following method was found to be more convenient than that described by Clemons and Cocker (*loc. cit.*). Ethyl methylmalonate (27 g.) in dry benzene (20 c.c.) was added dropwise to powdered sodium (3.55 g.) in dry benzene (50 c.c.), and the reaction was continued until the sodium had disappeared. Then 2-chlorocyclohexanone (20 g.) was slowly added with stirring, and the mixture was stirred and refluxed for 8 hours. It was diluted with water and the benzene layer was separated, dried, and distilled. The ester (18 g.) was collected at 158–162°/3–4 mm., but all attempts to get a good analytical specimen failed. It was therefore hydrolysed under reflux for 2 hours with a mixture of potassium hydroxide (12 g.), methyl alcohol (90 c.c.), and water (30 c.c.). Methyl alcohol was removed under reduced pressure, and the cooled residue was acidified with dilute sulphuric acid and extracted with ether from which 2-ketocyclohexyl- α -propionic acid (5 g.) was obtained, m. p. 133–134°. It crystallised from water (charcoal) as colourless plates, m. p. 134.5–135.5° (Found: equiv., 172. Calc. for $C_9H_{14}O_3$: equiv., 170). Its 2:4-dinitrophenylhydrazones crystallised from alcohol as yellow needles, m. p. 244° (decomp.) (Found: C, 51.3; H, 5.5. Calc. for $C_{19}H_{18}O_8N_4$: C, 51.4; H, 5.1%).

Lactone (V).—The above keto-acid (17.5 g.) was heated under reflux for 2 hours with acetic anhydride (60 c.c.). Acetic anhydride was removed under reduced pressure and the residue was extracted with ether. The extract was washed several times with sodium hydrogen carbonate solution, dried, and distilled, to give the required lactone as a highly refractive liquid, b. p. 133–134°/3 mm. (Found: C, 70.5; H, 7.8. $C_9H_{12}O_3$ requires C, 71.0; H, 7.9%). This lactone was somewhat less soluble in water than its lower homologue, but it was readily and quantitatively saponified with 5–10% methyl-alcoholic potash to 2-ketocyclohexyl- α -propionic acid, m. p. and mixed m. p. 135°.

Attempted hydrogenation. The above lactone (0.9763 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0.5 g.) was hydrogenated at 15°/745 mm. 17.5 C.c. of hydrogen were absorbed in about 15 minutes, and then absorption ceased. Adams's catalyst (0.1 g.) just previously reduced was later introduced and a further 30.0 c.c. of hydrogen was absorbed, but even after further shaking overnight no appreciable further absorption took place. On removal of the acetic acid and alkaline hydrolysis of the residue, 2-ketocyclohexyl- α -propionic acid (0.7 g.), m. p. 135°, was recovered.

2-Hydroxycyclohex-1-enyl- α -isobutyrolactone (VI; $R_1 = R_2 = \text{Me}$).—(a) From 2-acetoxycyclohexanone. Clean and bright zinc wool (3.2 g.; 2.1 g.-atoms) was added in portions to 40 c.c. of a mixture of 2-acetoxycyclohexanone (3.5 g.; Bergmann and Gierrth, *Annalen*, 1926, **448**, 48), ethyl α -bromoisobutyrate (4.4 g.), iodine (0.05 g.), and dry benzene (85 c.c.), and the whole was brought to the boil, under reflux, with stirring. Reaction set in, and after 10 minutes the remainder of the benzene solution was added dropwise to the stirred mixture. Stirring and refluxing were then continued for 3 hours. The mixture was cooled and added to 10% sulphuric acid and ice, and, after shaking, the benzene layer was separated, washed with 5% sodium hydrogen carbonate solution, dried, and distilled, the fraction b. p. 139–140°/6 mm. being collected. This was again distilled and the ester collected as a colourless viscous liquid (4.6 g.), b. p. 127–130°/3–4 mm. (Found: C, 62.4; H, 8.9. $\text{C}_{14}\text{H}_{24}\text{O}_5$ requires C, 61.8; H, 8.8%). The ester (3.55 g.) was hydrolysed by heating under reflux for 3 hours with potassium hydroxide (2.5 g.) and methyl alcohol (50 c.c.). Methyl alcohol was removed, and the residue was dissolved in water, clarified with charcoal, and acidified with 20% sulphuric acid. The solution was then saturated with ammonium sulphate and extracted with ether from which a solid, m. p. 69–73°, was obtained. It was crystallised from ligroin (b. p. 40–60°), and the lactone of 1:2-dihydroxycyclohexyl- α -isobutyric acid (XI) was obtained as colourless needles, m. p. 107–108° (Found: C, 65.6; H, 8.3. $\text{C}_{10}\text{H}_{16}\text{O}_5$ requires C, 65.2; H, 8.7%). Attempted dehydration of the ester (3.2 g.) was carried out by boiling for 3 hours with acetic anhydride (6 g.) and fused sodium acetate (3 g.). On hydrolysis of the product only (XI) was obtained. Again dehydration was attempted by heating the ester (2.0 g.) with pyridine (20 c.c.) and phosphoryl chloride (7 c.c.) at 150–160° for 4 hours. The reaction mixture was then cooled and poured into ice and sulphuric acid and the mixture was exhaustively extracted with ether. From the extract a small quantity of oil, b. p. 100–130°/3 mm., was obtained, from which by hydrolysis (XI) was produced. The lactone (XI; 0.5 g.) was heated on the water-bath with 30% sulphuric acid in 50% alcohol (10 c.c.) for 3½ hours. The product was an oil which was immediately saponified with 10% sodium hydroxide and the small amount of acidic product was extracted with ether. It yielded a 2:4-dinitrophenylhydrazone which had m. p. 250°, undepressed by that of authentic 2-ketocyclohexyl- α -isobutyric acid prepared as described below (c).

(b) From 2-carbethoxycyclohexanone. 2-Carbethoxycyclohexanone (13 g.) was added dropwise to sodium ethoxide from sodium (1.76 g.) and alcohol (48 c.c.). The solid sodio-derivative was cooled and with stirring ethyl α -bromoisobutyrate (15 g.) was slowly added and the mixture was refluxed for 24 hours. Alcohol was then removed and the residue was diluted with water and extracted with ether, from which by distillation a fraction, b. p. 155–180°/2–3 mm., was obtained. On redistillation a fraction (5.3 g.) was collected at 170–178°/2–3 mm. This fraction was refluxed for 3 hours with a solution of potassium hydroxide (4 g.) in methyl alcohol (50 c.c.), methyl alcohol was distilled off, and the residue, after acidification was saturated with ammonium sulphate and extracted many times with ether. From this extract pimelic acid, m. p. 103–104° (Found: C, 52.5; H, 7.5; equiv., 73.2. Calc. for $\text{C}_8\text{H}_{12}\text{O}_4$: C, 52.5; H, 7.5%; equiv., 80), and another solid product were isolated. The latter consisted of hygroscopic needles. It was strongly acid but gave no carbonyl reactions. It was not investigated further.

(c) From 1-hydroxycyclohexyl- α -isobutyric acid. This compound was previously prepared by Wallach and Mallinson (*loc. cit.*) but experimental details were scanty. We adopted the following procedure. Clean and bright zinc wool (32 g.) was added in five equal portions to a stirred boiling mixture of cyclohexanone (40 g.), ethyl α -bromoisobutyrate (80 g.), iodine (0.05 g.), and benzene (150 c.c.). The mixture was heated with stirring for 3 hours, then cooled, poured on crushed ice, and shaken with 20% sulphuric acid (300 c.c.). The benzene layer was removed and the aqueous layer was further extracted with benzene and the combined benzene extracts were dried. The extract was distilled and the fraction, b. p. 134–136°/10–12 mm. (32 g.), collected. This consisted of ethyl 1-hydroxycyclohexyl- α -isobutyrate. The above ester (30 g.) was heated for 2½ hours at 150–160° with freshly fused potassium hydrogen sulphate (60 g.). The mixture was cooled and the paste extracted several times with ether. The ether extract was distilled and the fraction (13 g.), b. p. 130–136°/10–12 mm., collected. This was substantially ethyl cyclohex-1-enyl- α -isobutyrate. An earlier fraction (13 g.), b. p. 120–130°/10–12 mm., was the unhydrated ester. A mixture of the unsaturated ester (13 g.), potassium hydroxide (7.2 g.), and methyl alcohol (120 c.c.) was refluxed for 3 hours. The methyl alcohol was distilled off and the residue diluted with water and extracted with ether. The aqueous layer was then clarified with charcoal, acidified, and extracted with ether from which by distillation cyclohex-1-enyl- α -isobutyric acid (4.5 g.) was obtained as a viscous liquid, b. p. 154–160°/10–12 mm. It solidified on being kept, and crystallised from dilute alcohol as long colourless needles, m. p. 71–72° (v. Braun and Münch, *Annalen*, 1928, **465**, 52, give m. p. 69–71°). The acid (0.1 g.) in 10% sodium carbonate (20 c.c.) was treated at room temperature with saturated bromine water in excess. The opalescent liquid was then extracted with ether from which an oil was obtained which slowly solidified. It was purified by sublimation in a vacuum and the bromo-lactone was obtained as long prisms, m. p. 59–60° (Found: C, 49.2; H, 6.3. $\text{C}_{10}\text{H}_{16}\text{O}_5\text{Br}$ requires C, 48.6; H, 6.1%). This lactone had a strong camphoraceous odour; it was insoluble in cold sodium hydroxide but on being warmed with this reagent it rapidly decomposed giving a solution containing sodium bromide.

The above unsaturated acid (13.5 g.) was stirred and gently refluxed with 50% sulphuric acid (135 g.) for 6 hours. The dark gum which was produced on dilution with water was extracted with ether, and the extract was washed with 5% sodium carbonate and dried. On distillation two fractions were obtained: (i) b. p. 50°/10–12 mm. (4 g.), and (ii) b. p. 136–140°/10–12 mm. (4.3 g.). Fraction (i) was distilled at atmospheric pressure and collected at 155–157°. It was undoubtedly 1-isopropylcyclohexene (Found: C, 86.6; H, 12.3. Calc. for C_9H_{16} : C, 87.1; H, 12.9%). It gave a nitrosochloride which crystallised from benzene-ligroin as needles, m. p. 143–144°. Wallach and Mallinson (*loc. cit.*) give m. p. 129–130° (Found: C, 57.3; H, 8.4. Calc. for $\text{C}_9\text{H}_{16}\text{ONCl}$: C, 56.9; H, 8.4%). Fraction (ii) was the lactone of 2-hydroxycyclohexyl- α -isobutyric acid; it solidified on standing and had m. p. 48°. It was considered to be sufficiently pure for the further stages of the synthesis. The lactone (4.3 g.) was hydrolysed by boiling with sodium hydroxide (2 g.) in water (20 c.c.) for 30 minutes. The clear solution

was treated with a boiling solution of magnesium sulphate (6 g. of the heptahydrate) in water (40 c.c.). It was cooled, shaken thoroughly, and treated dropwise at 0° with bromine (5 g.). The mixture was then shaken for 24 hours, further portions of sodium hydroxide being added at intervals to ensure very slight alkalinity to phenolphthalein. The mixture was acidified and exhaustively extracted with ether, from which, after drying, a dark red solid was obtained. This was dissolved in a slight excess of sodium carbonate solution, boiled with charcoal, and filtered, and the hot solution was acidified with concentrated hydrochloric acid. The buff-coloured acid (2.7 g.) had m. p. 149–150° and was considered sufficiently pure for further work. A portion recrystallised from water (charcoal) was deposited as colourless prisms, m. p. 151–152°. This was undoubtedly 2-ketocyclohexyl- α -isobutyric acid (Found: C, 64.6; H, 8.6. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.6%). Its 2:4-dinitrophenylhydrazone crystallised from alcohol as yellow needles, m. p. 255–256° (decomp.) (Found: C, 52.3; H, 6.0. $C_{18}H_{20}O_8N_4$ requires C, 52.7; H, 5.5%). The above keto-acid (2.7 g.) dissolved in acetic anhydride (15 g.) was heated under reflux for 2 hours. The acetic anhydride was then removed under reduced pressure and the residue was extracted with ether. The extract was washed with sodium carbonate, dried, and distilled, and 2-hydroxycyclohex-1-enyl- α -isobutyrolactone (1.8 g.) was collected at 119–120°/10–11 mm. (Found: C, 71.5; H, 8.3. $C_{10}H_{14}O_3$ requires C, 72.3; H, 8.4%). On alkaline hydrolysis the keto-acid was regenerated.

Hydrogenation of the Lactone (VI; $R_1 = R_2 = Me$).—When the lactone (0.1996 g.) in glacial acetic acid (10 c.c.) mixed with palladised charcoal (0.2 g.) was submitted to hydrogenation at 16°/755 mm. no hydrogen was absorbed, but in a second experiment when lactone (0.1514 g.) in acetic acid (10 c.c.) mixed with Adams's platonic oxide catalyst (50 mg.) was reduced at 18°/758 mm., 7–8 c.c. of hydrogen were absorbed in 3 minutes and two molecules (43 c.c.) in 15 minutes. The acetic acid was then removed in a vacuum and a solid residue was obtained which was completely soluble in sodium carbonate with effervescence. The alkaline solution was shaken with charcoal, filtered, and acidified to give cyclohexyl- α -isobutyric acid as silvery plates, m. p. 77–78°, raised only to 80° on two crystallisations from dilute alcohol. This compound was identical with that obtained when cyclohex-1-enyl- α -isobutyric acid (0.2 g.) was hydrogenated in glacial acetic acid (15 c.c.) mixed with Adams's catalyst (0.06 g.) at 15°/751.5 mm. The total absorption, which took 15 minutes to complete, was 28.4 c.c., equivalent to 1 mol. of hydrogen per mol. of unsaturated acid. No hydrogenation took place with palladised charcoal as catalyst.

Attempts to Prepare 1-Hydroxy-3:4-dihydronaphthalene-2- α -isobutyrolactone.—The method adopted was the attempted condensation of ethyl α -bromoisobutyrate with ethyl 1-keto-1:2:3:4-tetrahydronaphthalene-2-carboxylate. α -Tetralone was prepared by the ring closure of γ -phenylbutyric acid with a mixture of phosphoric acid and phosphoric oxide (cf. Birch and Robinson, *J.*, 1945, 582); this method was more economical than the usual one involving the ring closure of γ -phenylbutyryl chloride (*Org. Synth.*, Coll. Vol. II, 569). α -Tetralone was converted into ethyl 1-keto-1:2:3:4-tetrahydronaphthalene-2-glyoxylate by a method similar to that employed by Hüchel and Goth (*Ber.*, 1924, 57, 1288), but decomposition of this compound to give the carboxylate was improved as follows. A mixture of the glyoxylate (7.5 g.) and finely powdered glass (7 g.) was heated in an oil-bath maintained at 190–195° for 2 hours. On cooling, the paste was extracted several times with ether from which the required ester (6 g.) was obtained as a colourless liquid, b. p. 153–155°/2 mm. (Found: C, 71.9; H, 6.5. Calc. for $C_{18}H_{14}O_3$: C, 71.6; H, 6.4%). The keto-ester (11.3 g.) was slowly added to a suspension of finely powdered potassium (2.1 g.) in xylene (50 c.c.) and the mixture was stirred and refluxed until all the potassium had dissolved. The bromo-ester (10.1 g.) was slowly added and the stirred mixture was heated under reflux for 24 hours. It was then cooled and poured into water, and the xylene layer separated and distilled. Five fractions were obtained, namely: (i) 60–70°/3 mm., (ii) 105–145°/3 mm., (iii) 155–160°/3 mm., (iv) 170–175°/3 mm., and (v) 180–185°/3 mm. Of these (i) was unchanged bromo-ester and (iii) was almost pure keto-ester. Fractions (iv) and (v) were separately hydrolysed for 5 hours with 8% methyl alcoholic potassium hydroxide, and from each a very small quantity of solid was obtained which by several crystallisations from dilute alcohol, was obtained as needles, m. p. 191–192° (Found: C, 69.5; H, 4.0%). It did not give a precipitate with 2:4-dinitrophenylhydrazine and was recovered unchanged after boiling with acetic anhydride for 2 hours. Its investigation was therefore abandoned.

Experiments with Dihydro- ψ -santonin.—All attempts to reduce dihydro- ψ -santonin in presence of palladised charcoal were unsuccessful, but it can be reduced in presence of Adams's catalyst (cf. Clemons and Cocker, *loc. cit.*).

Bromination. Dihydro- ψ -santonin (0.2 g.) in water (10 c.c.) containing sodium carbonate (0.5 g.) was slowly treated, with stirring, with bromine water (0.12 c.c. of bromine in 15 c.c. of water). On the addition of the first drop of bromine water a white precipitate was formed, and this was ultimately collected. It was washed with 10% sodium carbonate, then with water, and dried. On crystallisation from dilute alcohol the bromo-lactone was deposited as colourless prisms, m. p. 180° (decomp.) (Found: C, 52.6; H, 6.15; Br, 22.6. $C_{18}H_{21}O_4Br$ requires C, 52.2; H, 6.1; Br, 23.2%). This compound was readily decomposed on boiling with water yielding a solution containing hydrobromic acid.

Reduction of the bromo-lactone. Bromo-lactone (0.3 g.) in alcohol (5 c.c.) was refluxed with zinc dust (1.0 g.) for 4 hours. The hot mixture was filtered and the filtrate was evaporated to dryness. An oily residue was left and this was rubbed with 10% hydrochloric acid to remove zinc; a solid was thus obtained which, after being washed, was recrystallised from dilute alcohol; it separated as needles (0.2 g.), m. p. 187–188° undepressed with authentic dihydro- ψ -santonin. This compound was again obtained when the bromo-lactone was heated on the water-bath with zinc dust and acetic acid for 3 hours.

One of us (S. H.) desires to thank the Council of King's College for a Post-Graduate Scholarship. We also desire to thank Messrs. T. and H. Smith for a gift of ψ -santonin.

217. *The Kinetics of Aromatic Halogen Substitution. Part III. Iodination by Iodine Chloride.*

By L. J. LAMBOURNE and P. W. ROBERTSON.

Iodination by iodine chloride of, *e.g.*, acetanilide and anisole, like the corresponding brominations by bromine, shows third-order kinetics in acetic acid solution. When there is steric hindrance to the entry of the iodine atom into the benzene ring, as in pentamethylbenzene and *p*-tolyl methyl ether, there is concomitant iodine chloride-catalysed chlorination, and this has an inducing effect on the iodination. In chlorobenzene solution this side reaction becomes more prominent, occurring with a compound like anisole, for which steric hindrance is not to be expected.

THE use of iodine chloride as an iodinating agent has long been known, but its applicability is limited. Chattaway and Constable (*J.*, 1914, 105, 124) showed that in acetic acid solution, a 90% yield of the *p*-iodo-derivative is obtained from acetanilide. In iodination with iodine chloride the liberated hydrogen chloride combines with the reagent to form HICl_2 , with the result that the rate falls off rapidly during the course of the reaction, just as in the corresponding brominations owing to HBr_3 formation. This complicates the kinetic interpretation, necessitating measurements of the initial rates for the evaluation of the reaction order. The general conditions of such measurements have been discussed in Part I of this series (*J.*, 1943, 276). The following results were obtained for acetanilide, times (mins.) being shown for 10% iodine chloride absorption in acetic acid.

Temp.	M/20.		M/40.
24°	160	($n = 3.3$)	780
50	36	($n = 2.6$)	105

The order is approximately 3 at 24° and is less at 50°, an effect similar to that found in the bromination of this compound, for which orders, $n = 3.0$ (24°) and $n = 2.5$ (50°), were obtained at the same concentrations.

The iodination of anisole in acetic acid is accompanied by a certain amount of simultaneous chlorination. Equimolecular amounts of reactants, M/20, at 24°, ceased to react at 78% halogen absorption owing to the formation of HICl_2 . To such a solution a slight excess of anisole was added, and dry nitrogen passed through for 15 minutes. This procedure removed hydrogen chloride, but no chlorine, permitting a further gradual 8% halogen absorption, after which only iodine was left. The ratio of iodination to chlorination is therefore approximately 5 : 1, and on adding water to the solution, *p*-iodoanisole, m. p. 50–52°, was precipitated. The contribution of this concurrent chlorination is not sufficient seriously to affect the order of the iodination reaction, and the times, in acetic acid at 24°, indicate third-order kinetics :

	M/20.		M/40.		M/80.
Time ($x = 20$) at 24°	11.8	($n = 3.0$)	46.5	($n = 3.1$)	216
Time ($x = 20$) at 40°	4.8	($n = 3.0$)	19.0	($n = 3.0$)	77

Experiments with anisole in relative excess revealed that the reaction was unimolecular with reference to anisole and bimolecular with reference to iodine chloride.

Pentamethylbenzene, which was found to undergo bromination in acetic acid at a rapid rate approximately the same as that for anisole, reacts moderately rapidly with iodine chloride. With this compound a steric effect is to be expected, as the approach of the large iodine atom is hindered by the *ortho*-methyl groups. This reveals itself in the sense that the alternative chlorine substitution makes a greater contribution than in the reaction with anisole, where there is no steric hindrance. In M/20-solution in acetic acid at 24° there is 80% halogen absorption, corresponding with the relative contributions, iodination : chlorination = 3 : 1. Rate measurements show predominantly third-order kinetics in the experimental concentration range :

	M/40.		M/80.
Time ($x = 10$)	26	($n = 2.9$)	95

In *p*-tolyl methyl ether steric hindrance to the entry of the large iodine atom into the *o*-substitution is also to be expected, and with M/20-reactants in acetic acid at 24° the iodine chloride substitution stops at ~67% halogen absorption, corresponding with equal contributions of iodination and chlorination; disturbed third-order kinetics are observed :

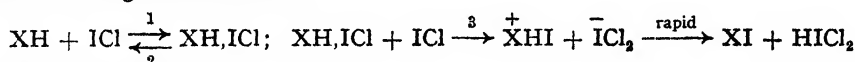
	M/20.		M/40.		M/80.
Time ($x = 20$)	86	($n = 3.3$)	420	($n = 2.7$)	1390

A summary of these iodine chloride reactions is now given :

	Acetanilide.	Anisole.	Pentamethylbenzene.	<i>p</i> -Tolyl methyl ether.
Concurrent chlorination ...	10%	20%	30%	50%
Relative rates, Br ₂ /ICl	950 : 1	350 : 1	150 : 1	70 : 1

Instead of the total rate of halogenation with iodine chloride becoming less (as compared with bromination) when there is steric hindrance, the reverse effect is observed. The alternative chlorine substitution, which is catalysed by iodine chloride, apparently exerts an inducing effect on the iodination by this reagent, and this becomes more considerable as the relative contribution of the chlorination increases. Other examples of induction in halogenation reactions have been reported (cf. *J.*, 1945, 509). On changing to chlorobenzene as solvent, the tendency for iodine chloride halogenation to proceed by the chlorination route becomes more pronounced, even when there is no steric hindrance; e.g., for anisole the contribution of the chlorination is 50%. Correspondingly, there is an increase in the velocity of the reaction, the relative rates, Br₂ to ICl, for anisole in chlorobenzene being 5 : 1 (in acetic acid solution the ratio is 350 : 1). This concurrent halogenation observed with iodine chloride should be still more pronounced with iodine bromide, as this compound is more dissociated than the chloride. According to Militzer (*J. Amer. Chem. Soc.*, 1938, 60, 256), phenol in carbon tetrachloride solution is exclusively brominated by iodine bromide. It is not, however, necessary to assume that this reaction proceeds according to the scheme $\text{XH} + \text{IBr} \longrightarrow \text{XBr} + \text{HI}$; $\text{HI} + \text{IBr} \longrightarrow \text{I}_2 + \text{HBr}$, for a mechanism involving iodine bromide-catalysed bromination will explain the experimental result.

The iodination of aromatic compounds by iodine chloride is analogous, not only to bromine substitution, but also to iodine chloride and bromine addition to unsaturated compounds. In acetic acid solution in the concentration region *M*/40, all four reactions show third-order kinetics, the order being reduced on rise in temperature owing to the incursion of a bimolecular reaction. It is concluded that the reaction mechanisms are similar (cf. *J.*, 1943, 279), taking place for iodination according to the scheme :



and for third-order kinetics

$$d[\text{XI}]/dt = (k_1 k_3 / k_2) [\text{XH}] [\text{ICl}]^2.$$

EXPERIMENTAL.

The compounds used were: anisole, b. p. 154.5°/760 mm.; *p*-tolyl methyl ether, b. p. 179°/760 mm.; acetanilide, m. p. 113.5°; pentamethylbenzene, m. p. 53.5°. The general technique was as previously described, the reactions being carried out with darkened bottles in a room with dim illumination. At 24° the iodine chloride solutions in acetic acid were found to be stable during the time of a reaction, but at higher temperatures there was a slight decrease in titre, necessitating a small correction. Herewith a typical set of measurements :

10 ml. anisole, *M*/40 + ICl, *M*/40; HOAc, 50°; 1 ml. samples titrated with KI and 0.01*N*-Na₂S₂O₃.

Time (mins.)	0	10	15	20	30	50
Titre (ml.)	4.98	4.62	4.46	4.25	3.98	3.62
Zero titre (ml.)	—	4.98	4.97	4.97	4.96	4.95

From the curve, *x* = 10, *t* = 15; second expt., *x* = 10, *t* = 14.

Experiments to determine relative contributions of anisole and iodine chloride in acetic acid at 24°; times (mins.), *x* = 10: A, *M* + ICl, *M*/20, *t* = 0.60; A, *M*/2 + ICl, *M*/40, *t* = 3.0; A, *M*/4 + ICl, *M*/40, *t* = 3.5; A, *M*/4 + ICl, *M*/80, *t* = 8.0: these gave *n* (anisole) 1.2, *n* (ICl) 2.2. The remaining measurements have been quoted in the text.

VICTORIA UNIVERSITY COLLEGE, WELLINGTON, N.Z.

[Received, November 21st, 1946.]

218. The Kinetics of Halogen Addition to Unsaturated Compounds. Part XII. Iodine Catalysis of Chlorine and Bromine Addition to Ethyl Cinnamate.

By H. D. C. WATERS, A. R. CAVERHILL, and P. W. ROBERTSON.

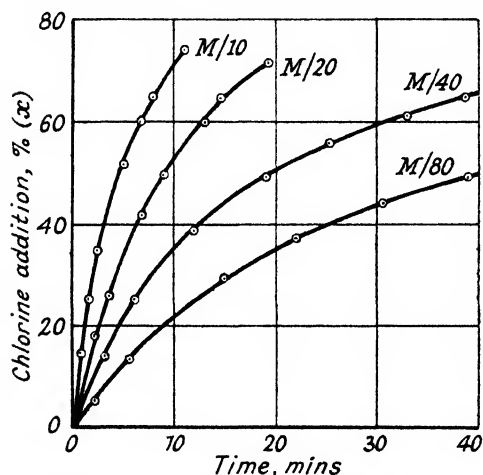
Iodine-catalysed addition of chlorine to ethyl cinnamate in carbon tetrachloride solution proceeds according to the expression $-d[\text{Cl}_2]/dt = k[\text{A}][\text{Cl}_2][\text{ICl}]$, and in the corresponding bromine reaction, $-d[\text{Br}_2]/dt = k[\text{A}][\text{Br}_2][\text{IBr}]$. At higher concentrations of added iodine,

the order for the chloride and the bromide becomes greater than unity. In the polar solvents chloroform and *o*-dichlorobenzene, the overall rate is one order less than in carbon tetrachloride, as for uncatalysed bromine addition. A general theory is proposed to explain the phenomenon of *trans*-halogen addition with inversion.

THE influence of iodine as a catalyst for bromine addition has long been recognised (Hertz and Mylius, *Ber.*, 1906, **39**, 3816; Bruner and Fischler, *A.*, 1914, ii, 260), but such rate measurements as have been made are insufficient to establish the kinetics of the reaction. Although iodine is known to catalyse chlorine addition to unsaturated compounds, there appears to be no record of any kinetic investigation of such reactions. However, Slator (*J.*, 1903, **83**, 729) has studied the kinetics of the reaction, $C_6H_6 + Cl_2$, in benzene as a solvent or diluted with carbon tetrachloride, with added iodine. The reaction proceeds with 70% substitution and 30% chlorine addition at a rate given by the expression, $-d[Cl_2]/dt = k[A][Cl_2][ICl]^2$, but the reaction was examined over only a limited iodine chloride concentration range.

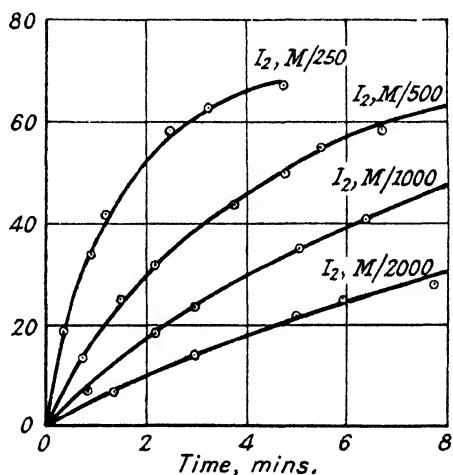
Just as the chlorination of benzene does not proceed in the absence of iodine, chlorine adds to ethyl cinnamate in dry carbon tetrachloride at a rate too slow to be measured, but with a small amount of added iodine the change goes rapidly to completion. At the end of the reaction the original amount of iodine is left, as is indicated by tintometric observation or titration of the

FIG. 1.



Ethyl cinnamate-chlorine, with I_2 , $M/1000$.

FIG. 2.



Ethyl cinnamate-chlorine, both $M/20$, with I_2 .

residual iodine. The kinetics of the reaction can be conveniently studied by rate determinations (a) with reactants, $A + Cl_2$, constant, and different amounts of iodine, or (b) with iodine constant and varying initial concentrations of $A + Cl_2$. The results of these experiments are shown in Figs. 1 and 2, the measurements being made in dry carbon tetrachloride under nitrogen at 24° .

The average orders, $\alpha = 10$ to $\alpha = 50$, for $A + Cl_2$ (Fig. 1) are: $M/10$ — $M/20$, $n = 2.0$; $M/20$ — $M/40$, $n = 2.0$; $M/40$ — $M/80$, $n = 2.0$. The reaction is thus bimolecular with respect to $A + Cl_2$, and the constancy of the bimolecular coefficients during the separate runs indicates the absence of autocatalytic disturbances. This is shown by a typical measurement, in carbon tetrachloride at 24° :

α	10	20	30	40	50
k_2 (reactants $M/20$, I_2 $M/1000$)	2.1	2.1	2.1	2.2	2.2

The average values of t_1/t_2 with different amounts of added iodine (Fig. 2) are: $M/2000$ — $M/1000$, 2.0; $M/1000$ — $M/500$, 2.0; $M/500$ — $M/250$, 2.4. On further addition of iodine the initial rates become too rapid for accurate measurements, but reach a maximum when the iodine chloride concentration is approximately equal to that of the chlorine, and then diminish.

The iodine is present almost entirely as chloride, and when its amount is small it does not appreciably alter the chlorine concentration, so these measurements are in accord with the rate expression

$$-d[Cl_2]/dt = k[A][Cl_2][ICl]$$

The increase in order with respect to iodine, when its amount becomes more considerable, will be discussed later.

The reaction between ethyl cinnamate and bromine in carbon tetrachloride (in nitrogen at 24°) was found to be not accurately reproducible under the conditions of the experiments, a result possibly due to the sensitiveness of this reaction to oxygen (cf. Bauer and Daniels, *J. Amer. Chem. Soc.*, 1934, 56, 378). Added iodine caused a very considerable acceleration of the rate, and the measurements, now found to be reproducible, were made by varying separately $A + Br_2$, and I_2 (Figs. 3 and 4).

The difference in appearance between Figs. 1 and 3 is due to the fact that bromination is a higher-order reaction than chlorination. The average orders, $x = 20$ to $x = 50$, for $A + Br_2$, are: $M/5-M/10$, $n = 2.9$; $M/10-M/20$, $n = 2.9$; $M/20-M/40$, $n = 3.0$. Special experiments,

FIG. 3.

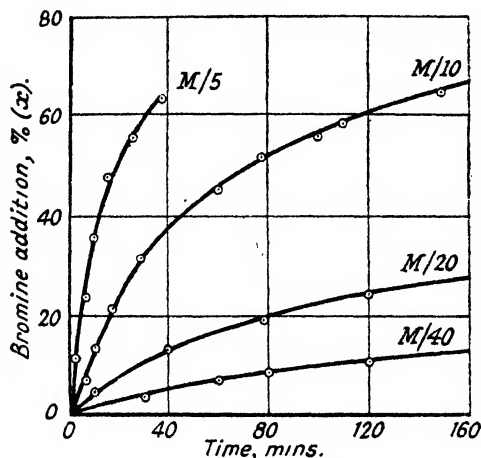
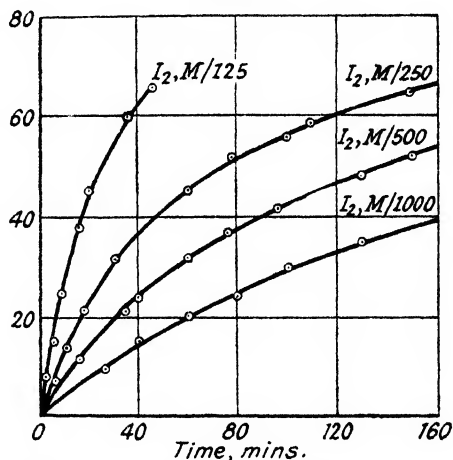
Ethyl cinnamate-bromine, with I_2 , $M/250$.

FIG. 4.

Ethyl cinnamate-bromine, both $M/10$, with I_2 .

A being varied and Br_2 kept constant, showed that the reaction was first order for A and second order for Br_2 . Correspondingly, the bimolecular coefficients fall as the reaction proceeds:

x	10	20	30	40	50	60
k_2 (reactants $M/10$, I_2 $M/500$)	0.16	0.155	0.15	0.145	0.135	0.125

The effect of varying the amount of added iodine is shown in Fig. 4, the average t_1/t_2 ratios being: $M/1000-M/500$, 1.9; $M/500-M/250$, 1.95; $M/250-M/125$, 2.7. As for the iodine-catalysed additions of chlorine, the order with respect to iodine is constant for low concentrations of added iodine, and subsequently increases. Iodine with bromine in carbon tetrachloride solution is almost entirely present as IBr , so these results correspond, for small amounts of iodine bromide, with the rate expression

$$-d[Br_2]/dt = k[A][Br_2]^2[IBr]$$

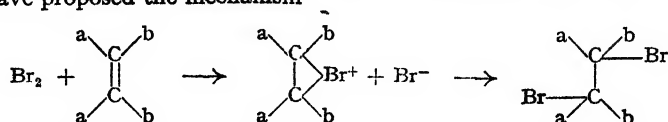
In polar aprotic solvents such as chloroform and *o*-dichlorobenzene, addition of bromine shows third-order kinetics (*J.*, 1945, 509). Added iodine in these solvents causes a relatively smaller catalysis than in carbon tetrachloride, and for small amounts of iodine the rate is given by the expression

$$-d[Br_2]/dt = k[A][Br_2][IBr]$$

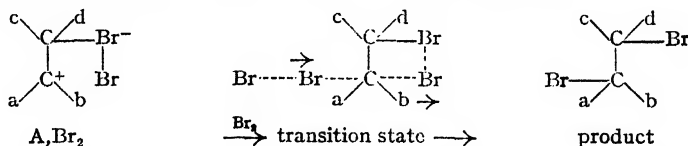
The iodine-catalysed addition of bromine to allyl benzoate in carbon tetrachloride has also been examined, with reactants $M/10$ and $M/20$, and iodine $M/500$ and $M/1000$. The average orders obtained were $A + Br_2$, $n = 2.8$; IBr , $n = 1.3$, so for this compound also the catalysed reaction can be regarded as a fourth-order reaction with one or more molecules of bromine replaced by iodine bromide. With greater amounts of added catalyst, the order for iodine bromide increases, but the reaction becomes too rapid for accurate measurement.

The addition of halogen to ethylenic compounds is a two-stage process, and to explain the

trans-addition with inversion that takes place, Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, 59, 947) have proposed the mechanism

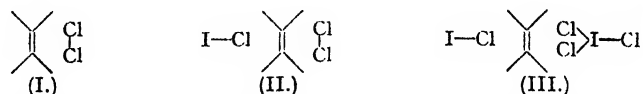


The discovery that addition of bromine may take place by a termolecular mechanism (*J.*, 1937, 335) was not inconsistent with this mode of formulation, as the result could be explained by the reaction proceeding: $A + Br_2 \longrightarrow A, Br_2 \xrightarrow{Br_2} ABr^+ + Br_3^- \longrightarrow ABrBr + Br_2$ (*J.*, 1943, 276). There are, however, certain formalistic difficulties in connection with Roberts and Kimball's theory. The Br^- released in the first stage must move to the reverse side of the positive ion to complete the process, and the model of the transition state reveals a condition of considerable strain. An alternative mechanism is now proposed, according to which the initial addition compound forms a four-atom ring (in which the strain is less than in a three-atom ring) and the change is completed by a second molecule of bromine:

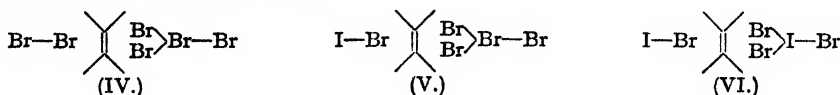


The formation of A, Br_2 is due to the electrophilic attack by Br_2 on A , and A, Br_2 is represented by one of its possible resonance structures. The dotted lines in the diagram of the transition state indicate bond lengths intermediate between covalent and ionic bonds, as suggested by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173), and the arrows show the direction of the movement of the bromine atoms. The model thus constructed fulfils the requisite conditions for minimum strain, the bonds $C-C$, $C-a$, and $C-b$ all being in one plane, and the direction $Br-C-Br$ at right angles to this plane. The criticism may be made, however, that with such a mechanism there should be a possibility of *cis*-addition also, and in fact this is actually found, more extensively indeed than suggested in general in writings on this subject. For instance, Liebermann and Finkenbeiner (*Ber.*, 1895, 27, 2235) have shown that addition of chlorine to cinnamic acid in the dark in carbon tetrachloride takes place almost entirely by the *cis*-mechanism, whereas in the light the high m. p. isomer formed by *trans*-addition is obtained. No reference was made to the drying of the solvent, so the reaction appears to have been catalysed by water. In the corresponding addition of bromine to cinnamic acid in the same solvent, in the dark there is 37% *cis*-addition, which becomes reduced to 13% when the reaction takes place in light (Michael, *Ber.*, 1901, 34, 3663). When steric hindrance to addition becomes considerable, e.g., in *o*-nitrostilbene, addition of bromine may take place preferentially by the *cis*-mechanism (Peiffer, *Ber.*, 1915, 48, 1051).

With a small amount of added iodine we find that addition of chlorine to cinnamic acid, in the dark, takes place with the formation chiefly of the *trans*-addition product. These observations suggest the following modes of reaction mechanism for addition of chlorine to ethyl cinnamate: (I), no iodine, *cis*; (II), a small amount of iodine, *trans*; (III), a larger amount of iodine, *trans*, the iodine trichloride being represented by one of its possible resonance structures.



With the higher-order addition of bromine to ethyl cinnamate the process becomes more complicated, one or two molecules of bromine being replaced in the catalysed reactions by iodine bromide. This is illustrated by the following representations: (IV), fourth-order addition of bromine; (V), the same reaction catalysed by a small amount of iodine; and (VI), catalysed by a larger amount of iodine.



It was proposed (de la Mare, Scott, and Robertson, *J.*, 1945, 509) that the high-order bromine additions in the non-polar solvent carbon tetrachloride might be explained by a chain mechanism involving activated molecules, and it was considered that the iodine-catalysed reactions might have diagnostic value. Actually, it is difficult to devise a suitable chain mechanism involving iodine bromide molecules, and the kind of formulation suggested in the present communication appears on the whole a more likely mode of representation than a chain reaction for catalysed as well as uncatalysed bromine addition.

EXPERIMENTAL.

The materials and method were as previously described (*J.*, 1945, 511) except that chloramine-r was used instead of iodine in the back titration. Herewith the details of one of the measurements:

Ethyl cinnamate, $m/20 + Cl_2$, $m/20 + I_2$, $m/500$ in CCl_4 , at 24° .

Time (mins.)	0.88	1.80	2.73	4.80	9.80	12.20
Titre	1.55	1.98	2.34	2.77	3.36	3.61
Back titre	0.84	0.85	0.86	0.88	0.94	0.96
Cl_2 absorption, %	19	30	38	50	65	71

Our thanks are due to Mr. B. B. Marsh for the measurements in chloroform solution.

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[Received, November 21st, 1946.]

219. Potassium Fluoaluminates.

By F. A. PAINE and J. PEARSON.

The chemical composition of potassium cryolite, the synthetic analogue of the naturally-occurring (sodium) cryolite, does not correspond to the theoretical K_3AlF_6 , and certain manufactured batches have been found to be abnormally acid. Preliminary experiments had indicated that the salt was not stable in water; it was therefore desirable that the chemistry of the double fluorides of potassium and aluminium should be studied more fully, and the effect of water on potassium cryolite elucidated. Under normal conditions of manufacture, from aluminium and potassium fluorides or potassium hydroxide and "hexafluoaluminic acid" in aqueous solution, it is impossible to prepare a stable material corresponding to the true potassium hexafluoaluminate. A well-defined pentafluoaluminate, K_5AlF_6 , has been shown to exist, and evidence has been obtained for the existence also of a tetrafluoaluminate, $KAlF_4$. When it is expected that the hexafluoaluminate would be formed, there usually results a material in which the molecular ratio of potassium fluoride to aluminium fluoride is slightly less than 3 : 1. This is in agreement with some recently published work. The effect of water upon potassium cryolite has been shown to be, first, dissociation of the double salt into potassium fluoride and potassium pentafluoaluminate, followed by solution of the latter if the concentration of potassium fluoride in the aqueous phase is less than 0.15%. The concentration of potassium fluoride necessary to inhibit dissociation of potassium cryolite is of the order of 0.55%. The high acidities associated with some batches are to be attributed to the presence of an acid salt and not to hydrolytic effects.

DURING the examination of commercially prepared samples of potassium cryolite, nominally K_3AlF_6 , it was found that the potassium contents were much lower, and the aluminium contents much higher, than those calculated. In view of this discrepancy, a review was made of the possible methods of analysing such a substance, and many of them were tried with a view to ascertain whether the unexpected values were the result of unsuitable procedures. Since considerable significance has been attached to the results finally obtained, this review is given in an appendix. Table I gives the results of the examination of typical batches, in which allowance has been made for moisture and traces of sodium present, in comparison with the

TABLE I.

Sample	1.	2.	3.	4.	5.	6.	Calc., %.
Potassium	43.5	43.6	44.0	44.2	44.5	44.3	45.4
Aluminium	11.1	11.3	11.3	11.3	11.4	11.1	10.5
Fluorine	45.4	45.1	44.7	44.5	44.1	44.6	44.1

expected proportions. From the figures it will be seen that the molecular ratio of potassium fluoride to aluminium fluoride is less than the 3 : 1 expected.

A review of the literature (Mellor, "Inorganic and Theoretical Chemistry", Vol. V, pp. 306, 307; Gmelin, "Handbuch der Anorganische Chemie", Vol. 35, p. 450) shows that until recently potassium penta- and hexa-fluoaluminates have been regarded as stable compounds,

slightly soluble in water, containing potassium and aluminium fluorides in the molecular ratios 2 : 1 and 3 : 1, respectively. Apart from the relative proportions of water of crystallisation present in the salts, there had been no suggestion that any differences existed between the fluoaluminates prepared by melting together the components and those obtained by precipitation from aqueous solutions. During the course of the present investigation, a paper appeared (Brosset, *Chem. Abs.*, 1943, 37, 13), demonstrating from crystallographic studies that while potassium penta-fluoaluminate is first formed on adding potassium fluoride to solutions containing aluminium and fluoride ions, the compound produced in the presence of excess of potassium fluoride is not K_3AlF_6 but $K_{3-x}AlF_{6-x} \cdot xH_2O$, *i.e.*, potassium cryolite in which part of the potassium fluoride in the crystal lattice has been replaced by water. Brosset (*loc. cit.*) states that the only stable compounds obtainable by mixing aqueous solutions are K_3AlF_6 and $K_{2.8}AlF_{5.8}$.

EXPERIMENTAL.

In order to test the truth of Brosset's statement, potassium aluminium fluorides were prepared under carefully controlled conditions, and the resulting materials analysed by the methods detailed in the appendix. As a confirmation, conductometric titrations of aluminium fluoride with potassium fluoride in aqueous solution were conducted in the hope that these would reveal the existence of definite compound formation. These experiments are described below. Although the majority of samples of commercial potassium cryolite examined were essentially neutral in reaction, some were found to be abnormally acid, in that their suspensions in water required considerable additions (up to 60 mg. of potassium hydroxide per g. of solid) to render them neutral. The cause of this acidity has also been investigated. It had been anticipated, by analogy with sodium cryolite, that the solubility of potassium cryolite would be very low; reference may be found (Mellor, *op. cit.*) to figures quoted as solubilities of potassium cryolite, and as nothing is said to the contrary, it must be assumed that these refer to what were believed to be true solutions of the cryolite. It was found, however, that in certain circumstances, up to 22% by weight of potassium cryolite could be extracted by water, and qualitative and quantitative tests have indicated that this extractable material is potassium fluoride. In fact, an instance was brought to the authors' notice, in which the high solubility of potassium cryolite was explained on the assumption that the material consisted, not of the double salt, but of a mechanical mixture of the two components, from which water dissolved the more soluble potassium fluoride. In view of the fact that potassium cryolite is normally prepared from aqueous solution, it was decided to investigate fully the action of water on the compound. The results are reported later.

Except in the analytical procedures, it was found necessary to use paraffin-waxed glass or platinum vessels, since many of the reagents employed dissolved glass, etc., to an inconvenient extent.

Preparation of Potassium Fluoaluminates.—(i) *From potassium aluminate and hydrofluoric acid.* Solutions were prepared of potassium aluminate in potassium hydroxide in which the molar ratios of potassium to aluminium were 3 : 1 and 2 : 1. To avoid the presence of other anions, the solutions were made by dissolving weighed amounts of pure aluminium foil in standardised potassium hydroxide. These solutions were titrated with hydrofluoric acid, and the end-points determined potentiometrically with a calomel-antimony electrode combination. As would be expected, the end-points corresponded with the production of K_3AlF_6 and K_2AlF_6 , since the potential of the antimony-antimony oxide electrode was influenced only by the hydrogen-ion concentration of the systems. The precipitated solid phases were filtered off, washed with the minimum of cold water, dried, and analysed. The constitutions corresponded to the empirical formulae $K_{2.9}AlF_{5.9}$ and $K_{1.9}AlF_{4.9}$, respectively. This indicates that although K_3AlF_6 and K_2AlF_6 may have been formed initially, the hexafluoaluminate after brief washing had lost potassium fluoride, whilst the pentafluoaluminate had absorbed, from the finally acid solution, some hydrofluoric acid which had not been removed by washing and drying.

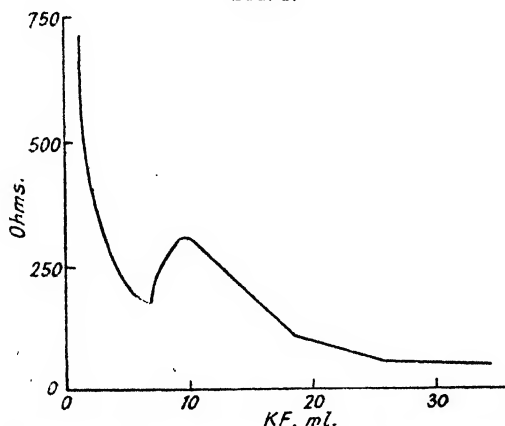
A solution of potassium aluminate (K : Al = 3 : 1) was neutralised with hydrofluoric acid, the potential of the antimony electrode then having a value corresponding to the middle of the potential-volume curve found in the first titration. This potential corresponded very closely with the change-point of methyl-red indicator. Similarly, hydrofluoric acid was neutralised with potassium aluminate. Finally, the aluminate was slightly over-neutralised with the acid. The solid phases produced in each case were filtered off, washed briefly, and dried. 1 G. of each was stirred with 100 ml. of cold water and titrated with N/20-potassium hydroxide solution, the end-points being determined potentiometrically. The acidities of the samples were found to correspond to 0.8, 2.7, and 56.8 mg. of potassium hydroxide per g., respectively. This indicates that in the presence of excess of hydrofluoric acid, potassium cryolite absorbs acid and does not readily part with it. This is probably due to the formation of a small proportion of an acid salt. This acid salt may be considered to be formed by the replacement of part of the potassium fluoride in the crystal lattice by hydrofluoric acid, in the same manner as Brosset (*loc. cit.*) has suggested for the replacement of potassium fluoride by water. The acidities observed in some commercial batches of potassium cryolite are thus to be ascribed to the presence of an acid salt, produced by the addition of slight excess of hydrofluoric acid, and not to hydrolysis. It has been found that a solution of aluminium fluoride in water is not acid.

(ii) *From potassium hydroxide and "hexafluoaluminic acid".* Addition of potassium hydroxide to "hexafluoaluminic acid" (a solution of aluminium fluoride or hydroxide in hydrofluoric acid in the correct proportions) and *vice versa* produced solids having properties, chemical and physical, identical with those of the products obtained above.

Conductometric Titrations of Potassium Fluoride and Aluminium Fluoride.—A saturated solution of aluminium fluoride in water was titrated with aqueous potassium fluoride and the conductivity of the aqueous phase determined when equilibrium had been established after each addition of titrant. Cell-resistance (*i.e.*, reciprocal of conductivity) was actually measured and plotted against volume of

potassium fluoride. The concentration of potassium fluoride was chosen so that the amount added made no significant change in the total volume. A typical curve obtained in this way is shown in Fig. 1. At the stage corresponding to 7.0 ml., precipitation of solid phase commenced, and the sudden rise in resistance at that point is to be attributed to the deposition of salt and not to the formation of a compound. The breaks at 9.3, 18.65, and 26.05 ml. correspond to the formation of KAlF_4 , K_2AlF_6 , and $\text{K}_{2.8}\text{AlF}_{5.8}$, respectively. This is in agreement with Brosset's work. It is noteworthy that Russian workers have examined synthetic and natural cryolite. Tananaev and Lechak (*Compt. rend. Acad. Sci. U.R.S.S.*, 1943, XLI, 3, 144) report that the ratio $\text{NaF} : \text{AlF}_3$ for Greenland cryolite is in the range 2.7—2.8. They

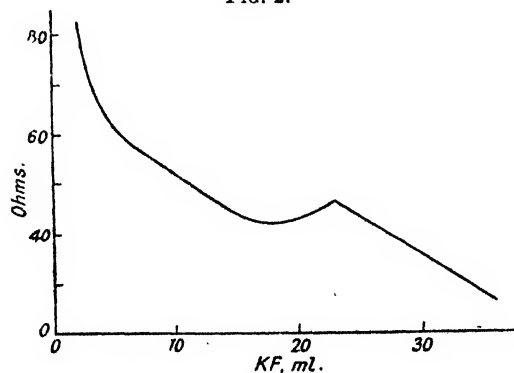
FIG. 1.



Conductometric titration of aluminium fluoride solution with potassium fluoride.

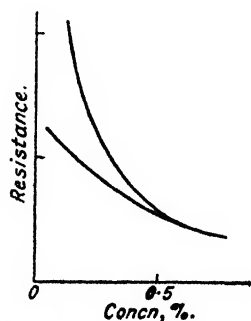
suggest a formula, for the natural and synthetic material, of $11\text{NaF} \cdot 4\text{AlF}_3$, which corresponds to $\text{Na}_{2.75}\text{AlF}_{5.75}$. Yatlow (*J. Gen. Chem. Russia*, 1937, 7, 2439) states that sodium cryolite is formed as a result of a reaction between the tetrafluoroaluminate, yielded initially by solutions of sodium fluoride and aluminium fluoride, and sodium fluoride. As the proportion of sodium fluoride is increased, the ratio of NaF to AlF_3 in the composition of the precipitate increases from 1 to 2.8. Yatlow has demonstrated the existence of sodium tetra- and penta-fluoroaluminates, but states that attempts to synthesise cryolite from aqueous solutions yielded a material of the composition $2.7\text{--}2.8\text{NaF} \cdot \text{AlF}_3$. The analogy with potassium fluoroaluminates is thus complete.

FIG. 2.



Conductometric titration of potash alum solution with potassium fluoride.

FIG. 3.



Conductivity of potassium fluoride solutions as influenced by addition of potassium cryolite.

No evidence was found for the formation of the hexafluoroaluminate when an aqueous solution of potash alum was titrated with potassium fluoride (see Fig. 2), the only significant break in the curve, at 23.2 ml., corresponding to formation of potassium pentafluoroaluminate. After the addition of 18 ml. of potassium fluoride solution, solid commenced to separate; the subsequent rise in resistance is to be attributed to this fact. This observation is not in accord with that of Berzelius (*Pogg. Ann.*, 1824, 1, 43) that potassium cryolite is formed from potash alum in the presence of excess of potassium fluoride. This point requires further examination, but it is of interest that a commercially prepared material, reputed to be potassium cryolite and made from potash alum and potassium fluoride, was found to consist of the hydrated pentafluoroaluminate, $\text{K}_2\text{AlF}_5 \cdot \text{H}_2\text{O}$.

The Effect of Water on Potassium Fluoaluminates.—A suspension of potassium cryolite (5 g. in 87.5 ml. of distilled water) was kept at 35° and stirred continuously, with precautions against loss by evaporation. At hourly intervals portions of the suspension were withdrawn, the solid phase removed, and the solution analysed. In every instance the only compound in solution was potassium fluoride. Its concentration increased gradually with time, until after about 6 hours it had become constant. At this stage there was present in every 10 ml. of solution 0.063 g. of potassium fluoride, *i.e.*, a 0.63% solution of potassium fluoride inhibited further dissociation of the hexafluoroaluminate to pentafluoroaluminate and fluoride.

The conductivities of solutions of potassium fluoride of various concentrations were determined. To fixed volumes of these solutions was added a standard weight of potassium cryolite (two typical commercial materials, $K_{2.7-2.8}AlF_{5.7-5.8}$ were used). The liquid was stirred until no further change in conductivity occurred. The initial and final conductivities (as resistance of a nominal volume of solution) were plotted against the concentration of the original solutions. The curves for the two samples were identical and are shown in Fig. 3. It will be seen that the two branches of the graph merge at a concentration of 0.55 to 0.60%. Since at concentrations below 0.55% the conductivity of a potassium fluoride solution was increased by the addition of potassium cryolite, it follows that dissociation of the cryolite had occurred. At concentrations of 0.60% and above, no alteration in conductivity was observed; no dissociation of the cryolite had taken place. This value for the inhibiting concentration is in good agreement with that found by analysing aqueous extracts; the conductivity measurements were carried out at 20° as against 35° used in the extraction method.

The above-mentioned samples of potassium cryolite and a sample of anhydrous potassium pentafluoroaluminate were used to study further the effect of water. 5 G. of each were suspended in 500 ml. of distilled water and shaken at room temperature until equilibrium was reached. The solid residues were removed and dried. The clear solutions and portions of the solids were analysed. 3 G. of the remaining solids were each suspended in 300 ml. of water and treated as above. The first extraction with water removed from each of the cryolites approximately 22% of potassium fluoride and left a residue with a composition approximating to K_2AlF_6 . The first aqueous extraction of the potassium pentafluoroaluminate removed only 13.3%, and this was found to be of a composition identical with that of the starting material and of the solid residue. The second extraction removed from each sample 13.2% of pentafluoroaluminate, leaving a solid of the same composition. It will thus be seen that the action of water on potassium cryolite is to dissociate and dissolve away potassium fluoride and then to take into solution the pentafluoroaluminate. Experiments conducted with solutions of various concentrations of potassium fluoride showed that the concentration required to prevent the solution of the pentafluoroaluminate is about 0.15%, *i.e.*, slightly less than the 0.22% resulting from the first water-extraction of the cryolite samples.

Appendix.

Analysis of Potassium Fluoaluminates.—(i) *Potassium.* Any method which involves preliminary separation of aluminium with ammonia or ammonium salts, etc., is liable to give low results owing to losses by adsorption on the precipitated alumina, by spitting during evaporation of solutions to dryness, and by decrepitation during heating to expel ammonium salts. Estimation as perchlorate, without separation of aluminium, avoids these losses, and has been found to give results in general higher than those obtained when potassium is estimated as sulphate, a method subject to the above-mentioned disadvantages. Some comparative figures are:

Sample	(a)	(b)	(c)	(d)	(e)	(f)
K, % (determined as K_2SO_4)	42.9	42.5	43.2	43.5	43.5	43.9
K, % (" " $KClO_4$)	43.4	43.8	43.9	43.8	43.5	44.1

(ii) *Aluminium.* Time is saved if aluminium is determined in the solution as used for the potassium estimation. This can be accomplished by precipitation with 8-hydroxyquinoline. Results are identical with those obtained when the aluminium is estimated as alumina; the use of oxine is to be preferred since the aluminium content of the "oxinate" is much smaller than that of alumina, and accidental impurities in the precipitate are of less importance.

(iii) *Fluorine.* Various modifications of the method involving titration with thorium nitrate have been examined. All suffer from the drawback that the end-point of the titration, using sodium alizarinsulphonate as indicator, may be uncertain and difficult to assess, though in the hands of an experienced operator accurate results are obtainable. The estimation as lead chlorofluoride is simpler; the distillation is easy to control, the weight of the sample taken is fairly large, and the estimation may be finished gravimetrically or volumetrically as desired, identical results being obtained by either method. Volumetric estimation was not employed in view of the consumption of silver nitrate. It should be noted that preliminary melting of the material with fusion mixture, as recommended by certain authorities, is not only unnecessary, but leads, in fact, to low results, as shown by the following figures:

F, % with fusion	44.6	44.0	44.3
F, % without fusion	45.2	44.5	44.3

It was found that fusion of potassium cryolite alone at temperatures above 900° leads to loss in weight, and also that sodium fluoride is volatile on heating.

(iv) *Sodium.* When it is desired to determine sodium content, it is necessary to decompose the cryolite with sulphuric acid, remove the aluminium, and use zinc uranyl acetate as precipitant.

The authors wish to thank the Chief Scientific Officer, Ministry of Supply, for permission to publish this paper.

220. Unsaturated Lactones. Some Esters of Aconic and Coumalic Acids.

By N. R. CAMPBELL and J. H. HUNT.

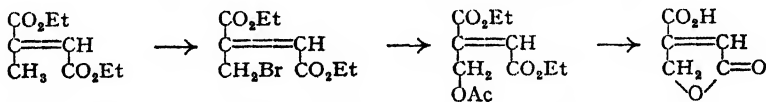
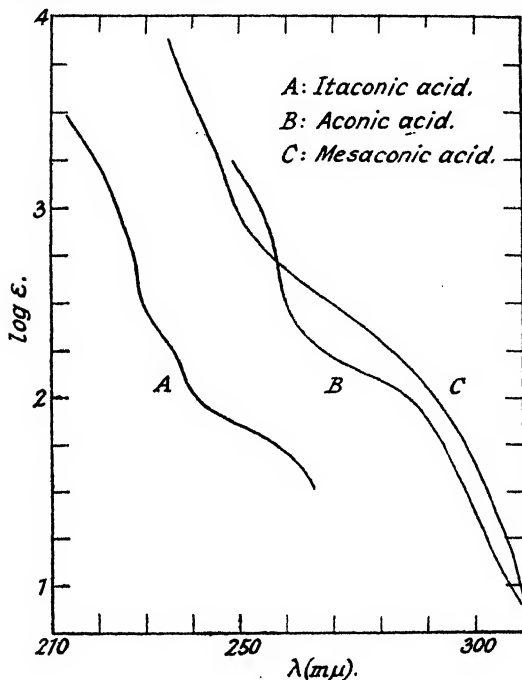
Aconic acid has been synthesised by a new method, which affords positive evidence for its acceptance as a β -substituted $\alpha\beta$ -butenolide. The older method of preparation has been developed, and a series of esters of aconic and coumalic acids prepared. The results of simple toxicity tests on the acids and their esters are given.

AMONG the simpler unsaturated lactones examined by Chen, Elderfield, Steldt, and Fried (*J. Pharmacol.*, 1942, **74**, 381) for cardioactivity, the methyl and ethyl esters of coumalic acid were

noteworthy for some positive result. It was considered desirable to extend this series of esters and to compare them biologically with a similar, related, series of esters of aconic acid.

The structure of coumalic acid is well established and probably beyond doubt, but there has been no positive evidence in support of the normally accepted $\beta\gamma$ -position of the double bond in aconic acid. The structure of this acid was given by Fittig and Beer (*Annalen*, 1883, **216**, 92) as β -carboxybutenolide, but they were unable to allocate an exact position to the double bond. We have now prepared the $\alpha\beta$ -acid by a method which does not involve conditions likely to cause migration, and have identified it with aconic acid prepared by the usual method from itaconic acid.

This new method of preparation involved bromination of the methyl group of diethyl mesaconate (diethyl methylfumarate) by means of *N*-bromosuccinimide, replacement of the bromine by an acetoxy-group under mild conditions, hydrolysis with barium hydroxide, and cyclisation by warming with water.



This evidence of structure brings aconic acid into line with the series of substituted butenolides which includes the aglycones of the digitalis and strophanthus groups of heart-poisons. The latter were also considered to be $\beta\gamma$ -butenolides before the work of Elderfield, Paist, Blout, and Uhle (*J. Org. Chem.*, 1941, **6**, 273) who produced evidence suggesting the present accepted $\alpha\beta$ -structure.

We have examined the ultra-violet absorption of aconic acid and compared the results with those obtained by Bielecki and Henri (*Ber.*, 1913, **46**, 2602) on mesaconic and itaconic acids, which are open-chain analogues of the two possible structures for aconic acid; we find that the absorption of aconic acid corresponds more closely to that of the fully conjugated isomer, thereby supplying further evidence for the $\alpha\beta$ -disposition of the double bond in aconic acid (see Fig.).

The preparation of aconic acid from itaconic acid was also studied. Itaconic acid was prepared by pyrolysis of citric acid (*Org. Synth.*, 1943, Coll. Vol. 2, 3 68); the isolation of acetone as a by-product together with approximately the theoretical volume of carbon monoxide indicated that acetonedicarboxylic acid was among the primary products of pyrolysis. Itaconic acid was brominated and the resulting "itadibromopyro-tartaric acid" (not isolated) converted into sodium aconate by a modification of the method used by Meilly (*Annalen*, 1874, **171**, 153), giving a greatly improved yield.

Esters of coumalic acid have been prepared by von Pechmann (*Annalen*, 1891, **264**, 279), Ruzicka (*Helv. Chim. Acta*, 1921, **4**, 504), and Caldwell, Tyson, and Lauer (*J. Amer. Chem. Soc.*, 1944, **66**, 1483). The method employed has generally involved treatment of a sulphuric acid solution of coumalic acid with the required alcohol, the coumalic acid being frequently prepared *in situ* from malic acid. We have employed both versions of this method and have also used much smaller (catalytic) quantities of sulphuric acid with azeotropic removal of water. Replacement of sulphuric acid by hydrogen chloride was not successful. We have compared the yields of one ester by the four methods; the first gave a considerably higher yield than the others.

The methyl and ethyl esters of aconic acid have been described by Meilly (*loc. cit.*), Reiter and Bender (*Annalen*, 1905, **339**, 316), and Wislicenus, Böklen, and Reuthe (*ibid.*, 1908, **363**, 353). The most suitable method for preparation of aconic esters is by reaction of silver aconate with the appropriate alkyl halide, usually at elevated temperature. With the exception of the *n*-butyl ester, the aconates prepared have all been obtained as crystalline solids; the isopropyl ester has been obtained in liquid and solid forms, both with satisfactory analyses. Ethyl aconate was described by Wislicenus (*loc. cit.*) as a liquid; under identical conditions we obtained a crystalline product.

While Rast's method gave satisfactory results for the molecular weights of all coumalates prepared, the aconates showed values ranging from theoretical to three times theoretical. We have been unable to explain this, or to correlate these anomalous results with the existence of solid and liquid forms.

Biological Investigation.—As a result of solubility difficulties in testing of these and other compounds by the usual assay method for digitalis, we adopted a simple toxicity test, the assumption being made that high cardioactivity might be accompanied by high toxicity. The substances were dissolved or suspended in arachis oil and administered subcutaneously to mice; median lethal doses (L.D./50) were calculated from the number of deaths after four days.

Toxicities in the coumalate series appear to decrease with increasing length of the alkyl chain, rather than with increasing molecular weight; the level of toxicity in the aconate series was so low that massive doses would be required for any variations to become apparent. It seems improbable that notable toxicity or cardioactivity will be found among simple esters of either of these acids.

	L.D./50.		L.D./50.
Coumalic acid	0.8 mg./g.	<i>n</i> -Butyl coumalate	>1 mg./g.
Methyl coumalate	0.3 mg./g.	isoButyl coumalate	0.6 mg./g.
Ethyl coumalate	0.33 mg./g.	Benzyl coumalate	>1 mg./g.
<i>n</i> -Propyl coumalate	0.55 mg./g.	cycloHexyl coumalate	0.55 mg./g.
isoPropyl coumalate	0.4 mg./g.		

Aconic acid, methyl aconate, ethyl aconate, *n*-propyl aconate, isopropyl aconate, *n*-butyl aconate, isobutyl aconate, benzyl aconate, and cyclohexyl aconate, all showed L.D./50 > 1 mg./g.

EXPERIMENTAL.

Sodium Aconate.—Itaconic acid (260 g.) was stirred to a paste with water (340 c.c.), and bromine (320 g.) slowly added, the temperature not being allowed to rise above 50°. When all but a trace of bromine had disappeared, the solution was neutralised with sodium hydrogen carbonate (336 g.). The mixture was then heated to 50° on the water-bath and treated with a suspension of sodium carbonate (106 g., anhydrous) in water (158 c.c.) at 50°, added in small portions until the solution remained neutral to bromothymol-blue. The mixture was cooled and allowed to remain at 0° for 1 hour. The crystalline sodium salt was filtered off, washed with iced water and with 95% alcohol, and dried in a vacuum at 110°. Yield of anhydrous sodium aconate, 179 g. (59%).

Silver Aconate.—Sodium aconate (100 g.) was stirred with water (80 c.c.) and heated to 40°. Silver nitrate (112.5 g.) dissolved in warm water (40 c.c.) was added, the mixture cooled to 0°, and the crystalline precipitate filtered off, washed with iced water and methanol, and dried in a vacuum desiccator. Yield, 147 g. (94%).

Aconic Acid.—Anhydrous sodium aconate (10 g.) was suspended in dry ether (30 c.c.). Dry hydrogen chloride was then passed in with stirring, until a gain in weight of 3.0 g. was obtained. The mixture was left overnight, the solid (11.5 g.) filtered off and extracted with ether in a continuous extractor. Removal of solvent left 7.6 g. of aconic acid, m.p. 162°. A further 0.7 g. of impure aconic acid, m.p. 156°, was obtained by evaporation of the original mother liquor. Total yield, 97%.

Ethyl Aconate (cf. Wislicenus, *loc. cit.*).—Silver aconate (30 g.) and ethyl iodide (15 c.c.) were heated in a sealed tube at 100° for 4 hours. The contents of the tube were extracted with ether, the extract washed with sodium hydrogen carbonate solution and water and dried (MgSO₄), and the solvent removed. The residue (15.5 g.) was distilled at reduced pressure, 8.95 g. of partly crystalline material (b. p. 132°/15 mm.) being collected. The crystals were separated and recrystallised from methanol at -10°. Yield, 3.3 g.; m. p. 64° (Found: C, 53.87; H, 5.31; M, 478. Calc. for C₇H₈O₄: C, 53.51; H, 5.13%; M, 157).

n-Propyl Aconate.—Silver aconate (20 g.) was refluxed for 1½ hours with *n*-propyl bromide (20 c.c.), excess of bromide then distilled off, and the residue diluted with ether and filtered. The brown oil (10.1 g.) remaining after removal of the ether was distilled, yielding 4.4 g. of partly crystalline material (b. p. 80–88°/0.1 mm.) which was dried on a porous tile. The ester, recrystallised from benzene–cyclohexane, had m. p. 34° (Found: C, 56.2; H, 6.04; M, 286. $C_9H_{10}O_4$ requires C, 56.5; H, 5.92%; M, 170).

isoPropyl Aconate.—(a) Silver aconate (14 g.) and isopropyl bromide (10 c.c.) were heated in a sealed tube at 100° for 3 hours. The contents of the tube were extracted with ether and the ether and excess of isopropyl bromide removed by distillation, leaving a brown oil (5 g.). Distillation of this yielded the ester as a colourless oil (1.7 g.), b. p. 70–71°/0.1 mm., n_D^{20} 1.460 (Found: C, 56.4; H, 5.58; M, 213. $C_8H_{10}O_4$ requires C, 56.5; H, 5.92%; M, 170).

(b) isoPropyl iodide (14 c.c.) was added slowly to silver aconate (28 g.) and benzene (30 c.c.). On gently heating the mixture a violent reaction commenced, necessitating cooling. The mixture was then refluxed for 1½ hours and cooled. The insoluble material was filtered off, washed with benzene, and extracted with ether in a continuous extractor. The ethereal extract yielded acetic acid (4.0 g.). The benzene solution was washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). Removal of the benzene gave a brown oil (9.48 g.), which on distillation gave two fractions: (i) b. p. 88–92°/0.2 mm., (ii) b. p. 100–120°/0.1 mm. Fraction (ii) which was partly crystalline was dried on a porous tile and recrystallised from light petroleum (b. p. 40–60°); m. p. 80° (Found: C, 56.3; H, 5.81%; M, 172).

n-Butyl Aconate.—Silver aconate (12.7 g.) was heated with *n*-butyl iodide (8 c.c.) and benzene (20 c.c.) in a sealed tube at 100° for 1 hour. The product, treated as for *n*-propyl aconate, yielded the ester as a colourless oil (2.5 g.), b. p. 91°/0.1 mm., n_D^{20} 1.471 (Found: C, 58.8; H, 6.66; M, 491. $C_9H_{12}O_4$ requires C, 58.7; H, 6.57%; M, 184).

isoButyl Aconate.—Silver aconate (25.4 g.) was refluxed for 1½ hours with isobutyl bromide (14 c.c.) and benzene (30 c.c.). The mixture was diluted with ether, filtered, and the filtrate washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). After removal of the ether the crude oily product (9.8 g.) was distilled under reduced pressure. The fraction, b. p. 86–88°/0.1 mm., partly crystallised and was dried on a porous plate. The solid ester was recrystallised from light petroleum (b. p. 60–80°); m. p. 114° (Found: C, 58.7; H, 6.58; M, 200. $C_9H_{12}O_4$ requires C, 58.7; H, 6.57%; M, 184).

Benzyl Aconate.—Silver aconate (11.5 g.) was refluxed for 1 hour with benzene (20 c.c.) and benzyl chloride (8.4 c.c.). The filtered benzene solution was washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). After removal of the benzene the ester was distilled under reduced pressure, b. p. 140°/0.04 mm., and recrystallised from cyclohexane. Yield, 1.1 g.; m. p. 59–60° (Found: C, 66.03; H, 4.55; M, 384. $C_{10}H_{10}O_4$ requires C, 66.04; H, 4.62%; M, 218).

cycloHexyl Aconate.—Acetic acid (6.25 g.) was dissolved in cold concentrated sulphuric acid (10 c.c.), the solution cooled to 0°, and cyclohexanol (15.8 c.c.) added. The mixture was allowed to warm to 18°, left for 20 hours, then poured on crushed ice and extracted with ether. After being washed, dried, and freed from solvent, the ester was crystallised from pentane (3.4 g.) and recrystallised from light petroleum (b. p. 60–80°); m. p. 68° (Found: C, 62.88; H, 6.72; M, 295. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71%; M, 210).

isoPropyl Coumalate.—Malic acid (50 g.) was added slowly with stirring to fuming sulphuric acid (150 g.) containing 10% of sulphur trioxide, and the mixture heated on the water-bath until evolution of gas ceased. The mixture was then cooled and isopropyl alcohol (165 c.c.) added. After being heated on the water-bath for 1 hour under reflux, the mixture was cooled, poured on ice (200 g.), partly neutralised with sodium carbonate, left overnight, and filtered. The filtrate was extracted with ether, and the extract washed, dried and freed from solvent. The residual oil was distilled under reduced pressure. The fraction, b. p. 102–110°/0.1 mm., deposited crystals of the ester which were twice crystallised from light petroleum (b. p. 40–60°). Yield, 6 g.; m. p. 44° (Found: C, 59.4; H, 5.35; M, 171. $C_9H_{10}O_4$ requires C, 59.3; H, 5.41%; M, 182).

n-Butyl Coumalate.—Malic acid (100 g.), fuming sulphuric acid (300 g.), and *n*-butyl alcohol (200 c.c.) were brought into reaction by the method employed for isopropyl coumalate. After distillation of the crude reaction mixture, the fraction, b. p. 120–124°/0.1 mm., solidified on standing. The ester was twice recrystallised from light petroleum (b. p. 40–60°). Yield, 10 g.; m. p. 41° (Found: C, 61.4; H, 6.14; M, 191. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.16%; M, 196).

n-Propyl Coumalate.—(a) Malic acid (100 g.), fuming sulphuric acid (300 g.), and *n*-propyl alcohol (176 g.) were brought into reaction by the method employed for isopropyl coumalate. Yield of pure ester, 14 g. (20%).

(b) Coumalic acid (6.8 g.) was dissolved in concentrated sulphuric acid (13 g.) and cooled to room temperature. *n*-Propyl alcohol (13 g.) was added, and the mixture heated with occasional shaking, on the water-bath, under reflux for 1 hour and poured into iced water (50 c.c.). The solid was filtered off, washed, and dried (6 g.). The filtrate was extracted with ether and a further quantity of solid obtained, which was added to that previously obtained and distilled under reduced pressure. The fraction, b. p. 96–100°/0.1 mm., was crystallised from light petroleum (b. p. 60–80°). Yield of ester, 5 g. (57%); m. p. 59–60° (Found: C, 59.8; H, 5.74; M, 188. $C_9H_{10}O_4$ requires C, 59.3; H, 5.41%; M, 182).

(c) Coumalic acid (6.8 g.) was covered with *n*-propyl alcohol (13 g.) and saturated with dry hydrogen chloride at 0°. The mixture was allowed to warm to room temperature, and next day was poured into water. No ester could be isolated; unchanged coumalic acid (5 g.) was recovered.

(d) A mixture of coumalic acid (6.8 g.), *n*-propyl alcohol (10.6 c.c.), toluene (10 c.c.), and concentrated sulphuric acid (2 drops) was distilled slowly, the distillate being dried (K_2CO_3) and returned. After 3 hours toluene and excess of propyl alcohol were distilled off. Yield of ester, 3 g. (34%).

isoButyl Coumalate.—Coumalic acid (7.1 g.), concentrated sulphuric acid (15 g.), and isobutyl alcohol (17.5 c.c.) were brought into reaction by the method employed for *n*-propyl coumalate. The crude ester

was distilled and the fraction, b. p. 120—126°/0.1 mm., twice crystallised from light petroleum (b. p. 40—60°). Yield, 6 g.; m. p. 62° (Found: C, 61.1; H, 6.21; M, 199. $C_{10}H_{13}O_4$ requires C, 61.2; H, 6.12%; M, 196).

Benzyl Coumalate.—Silver coumalate (4.5 g.) (von Pechmann, *loc. cit.*) was refluxed for 1 hour with benzyl chloride (5 c.c.) and benzene (15 c.c.). The filtered benzene solution was washed and dried. Removal of the benzene left an oil (2.7 g.), which was distilled under reduced pressure, b. p. 140—150°/0.05 mm., and crystallised twice from ether. Yield of *ester*, 0.52 g.; m. p. 92° (Found: C, 67.9; H, 4.19; M, 238. $C_{13}H_{11}O_4$ requires C, 67.8; H, 4.35%; M, 230).

cycloHexyl Coumalate.—Coumalic acid (12.6 g.) was dissolved in concentrated sulphuric acid (25 c.c.) and the mixture cooled to 0°. cycloHexanol (45 c.c.) was added and the mixture allowed to warm to room temperature and left for 3 days. The mixture was worked up as under cyclohexyl aconate, yielding 6.5 g. of crude crystalline *ester* which after further crystallisation (charcoal) from light petroleum (b. p. 60—80°) had m. p. 70° (Found: C, 65.09; H, 6.46; M, 224. $C_{12}H_{14}O_4$ requires C, 64.8; H, 6.35%; M, 222).

Diethyl γ -Bromomesaconate.—(a) Diethyl mesaconate (71 g.) was refluxed with *N*-bromosuccinimide (71 g.) and carbon tetrachloride (213 c.c.) for 30 hours. The mixture was cooled, filtered, freed from solvent, and diluted with light petroleum (b. p. 40—60°) (200 c.c.) which precipitated traces of succinimide. After filtration and removal of solvent the *ester* was distilled, b. p. 91°/0.1 mm. Yield, 52 g. (Found: C, 39.8; H, 5.07; Br, 33.6. $C_8H_{13}O_4Br$ requires C, 40.77; H, 4.94; Br, 30.14%).

(b) Diethyl mesaconate (48.5 g.) was heated under reflux with *N*-bromosuccinimide (31 g.), carbon tetrachloride (50 c.c.), and benzoyl peroxide (2.4 g.) for 1 hour. The mixture was filtered and the filtrate washed and dried. After removal of solvent the residue (60.0 g.) was distilled; unchanged diethyl mesaconate (18.2 g., b. p. 60—65°/0.15 mm.) was followed by the main fraction, b. p. 94—98°/0.15 mm. (31.3 g.), which was redistilled; b. p. 72°/0.10 mm., n_D^{20} 1.485 (Found: C, 40.71; H, 5.04; Br, 31.3%). Repeated distillation of the *ester* failed to give a product with a correct bromine analysis.

Aconic Acid.—Diethyl γ -bromomesaconate (10 g.) was heated for 1 hour on the water-bath, under reflux, with potassium acetate (5 g. fused) in absolute alcohol (50 c.c.). The mixture was cooled and filtered, most of the alcohol distilled off, and the residue taken up in benzene. The resulting oil was distilled, 7.23 g. being collected, b. p. 96°/0.1 mm.

The crude acetoxy-derivative (4.2 g.) was stirred for 1½ hours at room temperature with water (50 c.c.), and barium hydroxide (8.15 g.) was gradually added. The slightly cloudy solution was filtered and treated with 5*N*-sulphuric acid (10.5 c.c.). After removal of the barium sulphate, the solution was heated at 70° for ½ hour and then gave a deep purple colour in the Legal test whereas no colour was produced before heating. Extraction with ether in a continuous extractor gave a mass of sticky crystals which were washed with a little dry ether. Yield, 0.6 g. of crystals, m. p. 164°, which did not depress the m. p. of aconic acid (Found: C, 46.84; H, 3.31. Calc. for $C_6H_4O_4$: C, 46.89; H, 3.14%). The methyl ester (from the silver salt and methyl iodide) had m. p. 82° and did not depress the m. p. of methyl aconate.

Our thanks are due to Prof. Buttle and to Dr. M. Vogt, both of the Pharmacology Dept., the College of the Pharmaceutical Society, for their co-operation in working out details of the toxicity test employed and for preliminary tests (not quoted here). All the biological results were determined by Dr. H. O. J. Collier of the Pharmacology Dept. of this Company, to whom our thanks are also due. Ultra-violet absorption determinations were kindly carried out by Mr. H. F. W. Kirkpatrick. We desire also to thank the Directors of Messrs. Allen & Hanburys Ltd. for permission to publish.

ALLEN & HANBURYS LTD., WARE.

[Received, November 27th, 1946.]

221. Pyrazine Derivatives. Part III. Conversion of Diketopiperazines into Pyrazine Derivatives. Synthesis of 2-Hydroxy-3:6-di-*sec*-butylpyrazine from isoLeucine.

By R. A. BAXTER and F. S. SPRING.

A method for the conversion of diketopiperazines (α -amino-acid anhydrides) into pyrazine derivatives is described. isoLeucine anhydride (IX) has been converted into 2-chloro-3:6-di-*sec*-butylpyrazine (XI) and thence into 2-hydroxy-3:6-di-*sec*-butylpyrazine (II), and similarly alanine anhydride (III) has been converted into 2-chloro- (IV) and 2-hydroxy-3:6-dimethylpyrazine (VII).

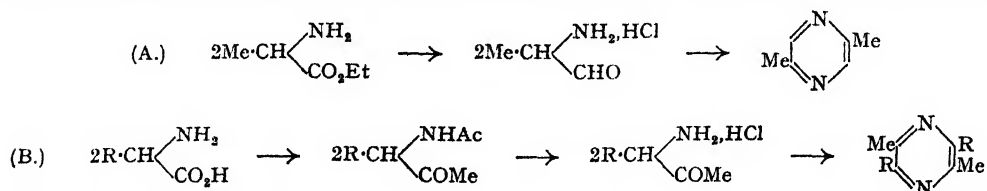
THE antibacterial substance aspergillic acid, for which the structure (I) has been suggested, is obtained from culture filtrates of the mould *Aspergillus flavus* using a medium containing an



amino-acid source such as tryptone. The present paper describes some preliminary experiments undertaken with the object of developing a synthetic route, starting from isoleucine, to

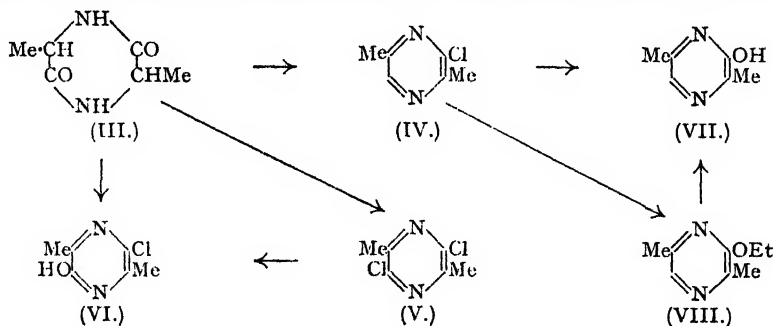
aspergillic acid or to the related deoxyaspergillic acid for which structure (II) has been suggested (for literature see Newbold and Spring, this vol., p. 373).

Two syntheses of pyrazine bases from α -amino-acids have been described. Reduction of the ethyl ester of alanine with sodium amalgam in the presence of hydrochloric acid gave the hydrochloride of α -aminopropaldehyde which when treated with alkali and mercuric chloride yielded 2 : 5-dimethylpyrazine in poor yield (A) (Neuberg, *Ber.*, 1908, **41**, 956; Fischer, *ibid.*, p.



1019). The second synthesis (B) consists in treatment of an α -amino-acid with acetic anhydride and pyridine to yield an α -acetamido-ketone which, when hydrolysed with hydrochloric acid, gave the corresponding α -amino-ketone hydrochloride. The latter when condensed with alkali in the presence of an oxidising agent gave a fully substituted pyrazine base (Dakin and West, *J. Biol. Chem.*, 1928, **78**, 745, 757).

Our method of approach to the problem consisted in a study of methods for converting a diketopiperazine (α -amino-acid anhydride) into an aromatic pyrazine derivative. The simplest reaction of this type would involve oxidation of a diketopiperazine to a dihydroxypyrazine, but so far as we are aware no transformation of this type has been reported. Abderhalden (*Z. physiol. Chem.*, 1924, **140**, 52; 1925, **143**, 128; 1925, **144**, 234) has shown that oxidation of glycine anhydride with potassium permanganate or with hydrogen peroxide and ferrous sulphate yields oxamide (cf. Ludtke, *Biochem. Z.*, 1925, **143**, 158), and according to Arai (*ibid.*, 1930, **226**, 233) glycine anhydride and phenylalanine anhydride on prolonged shaking with oxygen both yield urea. Goldschmidt and Steigenwald (*Ber.*, 1925, **58**, 1346) have shown that treatment of alanine anhydride with hypobromite yields an imidazolone derivative (cf. Goldschmidt, Wiberg, Nagel, and Martin, *Annalen*, 1927, **456**, 1). The present paper describes a method for the conversion of α -amino-acid anhydrides into halogen substituted pyrazine derivatives and the characterisation and conversion of these into hydroxypyrazine derivatives.



Treatment of *dl*-alanine anhydride (III) with phosphoryl chloride gives a mixture of 2-chloro-3 : 6-dimethylpyrazine (IV) and 2 : 5-dichloro-3 : 6-dimethylpyrazine (V). Separation of the two reaction products is relatively simple since the dichloro-derivative is not basic, whereas 2-chloro-3 : 6-dimethylpyrazine is soluble in 3*N*-hydrochloric acid. The formation of the monochloro-derivative (IV) from alanine anhydride does not involve an oxidation step, whereas the formation of 2 : 5-dichloro-3 : 6-dimethylpyrazine involves the oxidation of an intermediate dihydropyrazine derivative, a common step in many pyrazine syntheses. Treatment of *dl*-alanine anhydride with phosphoryl chloride in the presence of a tertiary base (dimethylaniline) gives only the monochloro-derivative, the intermediate dichlorodihydropyrazine presumably losing hydrogen chloride and thereby yielding the stable aromatic 2-chloro-3 : 6-dimethylpyrazine. 2-Chloro-3 : 6-dimethylpyrazine was not isolated from the reaction product obtained by treatment of *dl*-alanine anhydride with a mixture of phosphoryl chloride and phosphorus pentachloride (as oxidising agent), the reaction giving 2 : 5-dichloro-3 : 6-dimethylpyrazine in poor yield, together with a small quantity of 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine

(VI); the latter was the only isolated product of the reaction between *dl*-alanine anhydride and phosphorus pentachloride.

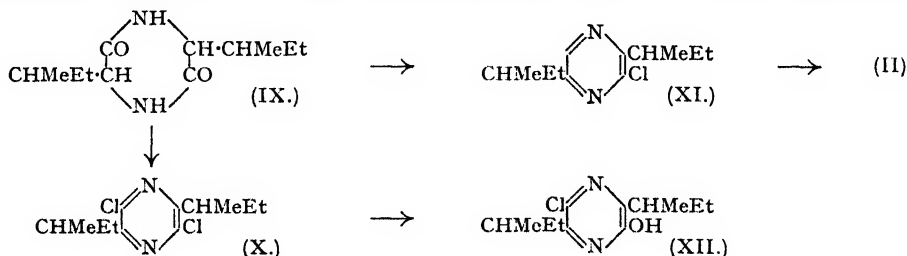
Prolonged treatment of 2-chloro-3:6-dimethylpyrazine with concentrated potassium hydroxide solution gives 2-hydroxy-3:6-dimethylpyrazine (VII) identical with that previously obtained by different synthetic methods (Baxter, Newbold, and Spring, this vol., p. 370). Less drastic methods for the replacement of the halogen atom by hydroxyl were sought, but so far we have not succeeded in replacing the halogen by an amino-group. Treatment of 2-chloro-3:6-dimethylpyrazine with alcoholic sodium ethoxide yields 2-ethoxy-3:6-dimethylpyrazine (VIII), hydrolysis of which with hydrochloric acid gives 2-hydroxy-3:6-dimethylpyrazine (VII).

Treatment of 2:5-dichloro-3:6-dimethylpyrazine with concentrated aqueous alkali yields 2-chloro-5-hydroxy-3:6-dimethylpyrazine (VI). This compound is soluble in alkali and reprecipitated from alkaline solution on acidification: its ultra-violet absorption spectrum is very similar to those of the simple hydroxypyrazine derivatives examined by Newbold and Spring (this vol., p. 373). 2-Chloro-5-hydroxy-3:6-dimethylpyrazine was recovered unchanged after treatment under drastic conditions with alcoholic ammonia. Although attempts to convert it into 2-hydroxy-3:6-dimethylpyrazine by reduction in alkaline solution with Raney alloy [Schwenk and Papa, *J. Org. Chem.*, 1944, 9, 1; *Ind. Eng. Chem. (Anal.)*, 1943, 15, 576] were unsuccessful, this transformation was effected by heating 2-chloro-5-hydroxy-3:6-dimethylpyrazine with solid potassium hydroxide. Treatment of 2-chloro-5-hydroxy-3:6-dimethylpyrazine with phosphoryl chloride using conditions which successfully convert *dl*-alanine anhydride into a mixture of 2-chloro- and 2:5-dichloro-3:6-dimethylpyrazine gives a very small yield of 2:5-dichloro-3:6-dimethylpyrazine, the starting material being largely recovered unchanged.

The reaction stages described above constitute a conversion of *dl*-alanine into 2-hydroxy-3:6-dimethylpyrazine. It was of great interest, therefore, to attempt to convert *dl*-isoleucine into 2-hydroxy-3:6-di-*sec*-butylpyrazine in order to compare the product with the racemate previously obtained by Newbold and Spring (*loc. cit.*) by a different synthetic route.

Ehrlich (*Ber.*, 1907, 40, 2550) obtained an *isoleucine* anhydride by heating *d*-isoleucine and commented that the compound was probably a mixture of isomers. Dutcher and Wintersteiner (*J. Biol. Chem.*, 1944, 155, 359) describe a racemic *isoleucine* anhydride prepared from *dl*-isoleucine. Using a modification of the method developed by Sannié (*Bull. Soc. chim.*, 1942, 9, 487) for the preparation of amino-acid anhydrides in which the α -amino-acid is heated with ethylene glycol, *dl*-isoleucine gave a *dl*-isoleucine anhydride in 49% yield. In a second method, α -bromo- β -methylvaleryl chloride was reacted with *dl*-isoleucine methyl ester hydrochloride and the product heated with alcoholic ammonia to yield a *dl*-isoleucine anhydride. Although the specimens of anhydride obtained by the two methods appear to be identical, it is clear that they may comprise different mixtures of isomers.

Treatment of *dl*-isoleucine anhydride (IX) with phosphoryl chloride gives a mixture of 2:5-dichloro-3:6-di-*sec*-butylpyrazine (X) and 2-chloro-3:6-di-*sec*-butylpyrazine (XI). The halogen substituents in these pyrazine derivatives are even less reactive than those in the corresponding dimethyl homologues. Thus 2-chloro-3:6-di-*sec*-butylpyrazine was recovered unchanged after prolonged refluxing with 20% potassium hydroxide solution, conditions which



converted 2-chloro-3:6-dimethylpyrazine into 2-hydroxy-3:6-dimethylpyrazine. When heated to 180° with powdered potassium hydroxide, however, 2-chloro-3:6-di-*sec*-butylpyrazine yielded 2-hydroxy-3:6-di-*sec*-butylpyrazine (II) identical with the racemate obtained previously from di-*sec*-butylpyrazine. 2:5-Dichloro-3:6-di-*sec*-butylpyrazine was also unchanged after treatment with concentrated aqueous alkali, but when heated with powdered potassium hydroxide it gave 2-chloro-5-hydroxy-3:6-di-*sec*-butylpyrazine (XII).

EXPERIMENTAL.

2:5-Dichloro-3:6-dimethylpyrazine.—A mixture of 2:5-diketo-3:6-dimethylpiperazine prepared from *dl*-alanine by the method described by Sannié (*loc. cit.*) (5 g.) and phosphoryl chloride (50 c.c.) was heated at 120° (bath temp.) for 20 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue triturated with ice-water. The solid was collected (filtrate *A*), washed with water, and dried over phosphoric oxide (yield, 1.3 g.). Sublimation of this material at 60–80°/2 mm. gave 2:5-dichloro-3:6-dimethylpyrazine as prisms, m. p. 73° (Found: C, 41.1; H, 3.7; N, 15.4. $C_8H_8N_2Cl_2$ requires C, 40.7; H, 3.4; N, 15.8%). Light absorption in alcohol: Maximum at 2975 Å., $\epsilon = 810$.

2-Chloro-3:6-dimethylpyrazine.—The filtrate *A* was treated with sodium carbonate solution until just alkaline and the mixture extracted with ether. The extract was dried, the ether removed, and the residue distilled to yield 2-chloro-3:6-dimethylpyrazine as an oil, b. p. 78°/15 mm. (1.4 g.), n_D^{20} 1.5284 (Found: C, 50.2; H, 4.8. $C_8H_8N_2Cl$ requires C, 50.5; H, 4.9%). 2-Chloro-3:6-dimethylpyrazine is soluble in 3*N*-hydrochloric acid. It forms a picrate, m. p. approx. 100°, and a chloroplatinate, m. p. > 360°, which are extremely soluble in the common solvents; this extreme solubility precluded their satisfactory purification.

Treatment of alanine anhydride (5 g.) with phosphoryl chloride (30 c.c.) and dimethylaniline (10 c.c.) for 20 minutes at 120° gave 2-chloro-3:6-dimethylpyrazine (1 g.). Difficulty was experienced in separating the product from the dimethylaniline; this may account for the low yield.

2-Chloro-5-hydroxy-3:6-dimethylpyrazine.—(a) A mixture of *dl*-alanine anhydride (5 g.), phosphorus pentachloride (5 g.), and phosphoryl chloride (15 c.c.) was refluxed for 30 minutes. Excess of phosphoryl chloride was removed by distillation and the residue triturated with water to give 2:5-dichloro-3:6-dimethylpyrazine (0.5 g.), m. p. and mixed m. p. 72–73°. The mother liquor was neutralised with sodium carbonate and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract gave a solid (0.8 g.) which, after crystallisation from benzene (needles) followed by sublimation, gave 2-chloro-5-hydroxy-3:6-dimethylpyrazine as needles, m. p. 224°. Although sparingly soluble in water, it is soluble in dilute sodium hydroxide and precipitated from this solution on acidification (Found: C, 45.6; H, 4.7. $C_8H_7ON_2Cl$ requires C, 45.4; H, 4.4%).

(b) A solution of 2:5-dichloro-3:6-dimethylpyrazine (0.5 g.) in dioxan (4 c.c.) and aqueous potassium hydroxide (10 c.c.; 20%) was refluxed for 20 hours. The solution was acidified with hydrochloric acid, the crystalline solid collected and purified by sublimation at 140°/1 mm. to give 2-chloro-5-hydroxy-3:6-dimethylpyrazine (0.35 g.) as needles, m. p. 224°, either alone or when mixed with the specimen described above (Found: N, 17.5. $C_8H_7ON_2Cl$ requires N, 17.7%). Light absorption in alcohol: Maxima at 2285 Å., $\epsilon = 10,000$ and 3330 Å., $\epsilon = 6,800$.

***dl*-isoLeucine Anhydride.**—(a) *dl*-isoLeucine (9 g.) was refluxed with ethylene glycol (54 c.c.) for 4 hours. The crude anhydride (2 g.) which separated on standing was purified by extraction with chloroform and evaporation of the chloroform filtrate. On crystallisation of the residue from alcohol, *dl*-isoleucine anhydride formed felted needles, m. p. 270° (sintering at 259°) (yield 49%) (Found: C, 63.5; H, 9.6. Calc. for $C_{11}H_{22}O_2N_2$: C, 63.7; H, 9.7%).

(b) An ice-cooled suspension of *dl*-isoleucine methyl ester hydrochloride (6.2 g.) in chloroform (80 c.c.) and α -bromo- β -methylvaleryl chloride (8 g.) was stirred and treated during 1 hour with a solution of *n*-butylpiperidine (22 g.) in chloroform (20 c.c.). The ice-bath was removed and the mixture stirred for a further hour. The chloroform solution was washed successively with water, dilute hydrochloric acid, sodium carbonate solution, and water. Evaporation of the dried chloroform solution under reduced pressure gave a semi-solid mass which did not crystallise completely. It was dissolved in ethanol (150 c.c.), the solution saturated with ammonia at 0° and heated at 180° for 8 hours. The reaction mixture was evaporated to dryness and the residue extracted with chloroform. The chloroform extract was evaporated and the product (1.4 g.) crystallised from alcohol to yield *dl*-isoleucine anhydride as needles, m. p. 270°, sintering at 280°. A mixture of this anhydride with a specimen prepared by method (a) softened at 260° and melted at 270° (Found: C, 64.2; H, 9.6; N, 12.6. Calc. for $C_{11}H_{22}O_2N_2$: C, 63.7; H, 9.7; N, 12.4%).

2:5-Dichloro-3:6-di-sec-butylpyrazine.—*dl*-isoLeucine anhydride (2.0 g.) was refluxed with phosphoryl chloride (20 c.c.) for one hour. The phosphoryl chloride was removed under reduced pressure and the product triturated with ice-water. The mixture was extracted with ether, the extract dried (Na_2SO_4), and the solvent removed. Distillation of the residue gave an oil (1.2 g.), b. p. 118°/12 mm. The oil was shaken with concentrated hydrochloric acid (15 c.c.) and the crystalline mass collected (0.15 g.) (filtrate *B*) and sublimed at 50°/1 mm. to yield 2:5-dichloro-3:6-di-sec-butylpyrazine as plates, m. p. 58–60° (Found: C, 55.3; H, 6.9; N, 10.9. $C_{12}H_{18}N_2Cl_2$ requires C, 55.2; H, 6.9; N, 10.7%).

2-Chloro-3:6-di-sec-butylpyrazine.—The filtrate *B* was diluted with water and neutralised with sodium carbonate solution. The mixture was extracted with ether and the extract dried and distilled; 2-chloro-3:6-di-sec-butylpyrazine (0.8 g.) was thus obtained as a colourless oil; b. p. 116°/12 mm., n_D^{20} 1.5030 (Found: C, 64.2; H, 8.5; N, 12.0. $C_{12}H_{18}N_2Cl$ requires C, 63.6; H, 8.4; N, 12.4%).

2-Ethoxy-3:6-dimethylpyrazine.—2-Chloro-3:6-dimethylpyrazine (1 g.) was treated with an alcoholic solution of sodium ethoxide (from 0.4 g. of sodium and 10 c.c. of ethanol) and the mixture heated under reflux for 4 hours. The solution was concentrated, diluted with water, and extracted with ether. The dried extract was distilled to give 2-ethoxy-3:6-dimethylpyrazine (0.7 g.) as a colourless oil, b. p. 81°/15 mm., n_D^{20} 1.4993 (Found: C, 62.8; H, 7.7; N, 18.5. $C_8H_{12}ON_2$ requires C, 63.2; H, 7.9; N, 18.4%). The picrate separated as prismatic needles from methanol, m. p. 108–109° (Found: C, 44.4; H, 4.2; N, 18.8. $C_{14}H_{16}O_7N_4$ requires C, 44.1; H, 3.9; N, 18.4%).

2-Hydroxy-3:6-dimethylpyrazine.—(a) 2-Chloro-3:6-dimethylpyrazine (1 g.) was heated under reflux with aqueous potassium hydroxide (20%; 10 c.c.) for 18 hours. The solution was neutralised (litmus) with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with benzene and the extract concentrated; 2-hydroxy-3:6-dimethylpyrazine (0.6 g.) then

separated as needles. After recrystallisation from the same solvent it had m. p. 208—210° either alone or when mixed with an authentic specimen.

(b) A solution of 2-ethoxy-3:6-dimethylpyrazine (0.6 g.) in hydrochloric acid (5*N*, 20 c.c.) was heated under reflux for 18 hours. The solution was evaporated to dryness, the residue dissolved in water, and the solution neutralised by the addition of sodium carbonate solution and evaporated to dryness. The residue was extracted with benzene and the extract concentrated; 2-hydroxy-3:6-dimethylpyrazine (0.4 g.), m. p. and mixed m. p. 208—210°, then separated as needles.

(c) 2-Chloro-5-hydroxy-3:6-dimethylpyrazine (0.5 g.) was heated at 180—200° for 5 hours with powdered potassium hydroxide (2 g.). The cold reaction product was dissolved in water, and the solution neutralised with dilute hydrochloric acid and then evaporated to dryness (reduced pressure). Extraction with benzene in the usual manner gave 2-hydroxy-3:6-dimethylpyrazine (0.2 g.) as needles, m. p. and mixed m. p. 208—210°. The picrate separated as blades from methanol, m. p. 180—182°, undepressed when mixed with the specimen described by Baxter, Newbold, and Spring (*loc. cit.*).

2-Hydroxy-3:6-di-*sec*-butylpyrazine.—2-Chloro-3:6-di-*sec*-butylpyrazine (0.5 g.) was heated with powdered potassium hydroxide (2 g.) for 4 hours at 180°. The reaction mass was dissolved in water and the solution extracted with ether. The alkaline solution was acidified; 2-hydroxy-3:6-di-*sec*-butylpyrazine (0.3 g.) then separated. It was collected and purified by sublimation at 110°/1 mm., and so obtained as small needles, m. p. 122—124°, not depressed when mixed with a specimen, m. p. 122—124°, prepared as described by Newbold and Spring (*loc. cit.*). Light absorption in alcohol: Maxima at 3250 Å., $\epsilon = 10,000$ and 2290 Å., $\epsilon = 9,100$.

2-Chloro-5-hydroxy-3:6-di-*sec*-butylpyrazine.—2:5-Dichloro-3:6-di-*sec*-butylpyrazine (0.3 g.) was heated with powdered potassium hydroxide (2 g.) for 4 hours at 160—180°. The mass was dissolved in water and unchanged dichloro-compound (0.2 g.) isolated by extraction with ether. Acidification of the solution with hydrochloric acid gave a solid which after sublimation at 90°/1 mm. gave 2-chloro-5-hydroxy-3:6-di-*sec*-butylpyrazine, m. p. 105—106°. It is freely soluble in the common organic solvents, but insoluble in water (Found: C, 59.4; H, 8.0. $C_{12}H_{13}ON_2Cl$ requires C, 59.4; H, 7.8%).

We thank Mr. J. J. Gallagher for assistance in some of the experiments described. Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Grant.

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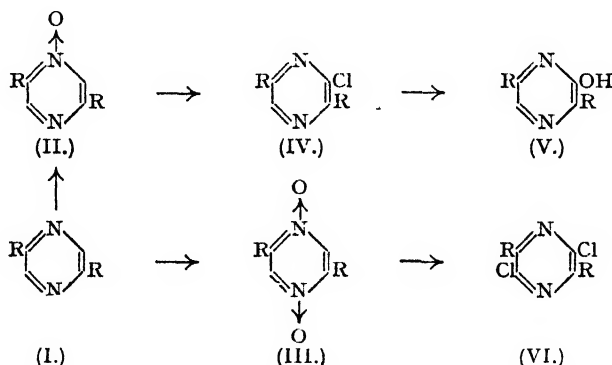
[Received, November 27th, 1946.]

222. Pyrazine Derivatives. Part IV. Pyrazine N-Oxides and their Conversion into Chloropyrazines.

By G. T. NEWBOLD and F. S. SPRING.

2:5-Dialkylpyrazines are readily oxidised to a mixture of the corresponding mono- and di-*N*-oxides. The mono- and di-*N*-oxides are smoothly converted into 2-chloro- and 2:5-dichloro-3:6-dialkylpyrazines respectively. Hydrolysis of the 2-chloro-3:6-dialkylpyrazine gives the corresponding 2-hydroxy-3:6-dialkylpyrazine. By this route, 3:6-di-*sec*-butylpyrazine yields a 2-hydroxy-3:6-di-*sec*-butylpyrazine identical with the racemate described by us in Parts II and III (this vol., p. 373, and preceding paper).

TREATMENT of 2:5-dimethylpyrazine (I, R = Me) with hydrogen peroxide in aqueous acetic acid gives 2:5-dimethylpyrazine *N*-oxide (II, R = Me) in 62% yield and 2:5-dimethylpyrazine di-*N*-oxide (III, R = Me) in 24% yield. Treatment of 2:5-dimethylpyrazine *N*-oxide with phosphoryl chloride gives 2-chloro-3:6-dimethylpyrazine (IV, R = Me) in 85% yield. Alkaline hydrolysis of the latter as described in the preceding paper yields 2-hydroxy-3:6-dimethylpyrazine (V, R = Me). This route to 2-hydroxy-3:6-dimethylpyrazine starting from 2:5-dimethylpyrazine is superior to that described by Baxter, Newbold, and Spring (this vol., p. 370).



2 : 5-Dimethylpyrazine di-*N*-oxide is converted by the action of phosphoryl chloride into 2 : 5-dichloro-3 : 6-dimethylpyrazine (VI, R = Me), identical with that described in the preceding paper. The yield, however, is low and is not increased by the use of sulphuryl chloride instead of phosphoryl chloride.

Treatment of 2 : 5-di-*sec*.-butylpyrazine (I, R = *sec*.-C₄H₉) with hydrogen peroxide gives a mixture of the corresponding mono- and di-*N*-oxides. 2 : 5-Di-*sec*.-butylpyrazine di-*N*-oxide (III, R = *sec*.-C₄H₉) is obtained in 64% yield, and on treatment with phosphoryl chloride it is converted into 2 : 5-dichloro-3 : 6-di-*sec*.-butylpyrazine (VI, R = *sec*.-C₄H₉), identical with that obtained from isoleucine anhydride. The mono-*N*-oxide (II, R = *sec*.-C₄H₉) was not isolated in a pure state; when treated with phosphoryl chloride it is converted into 2-chloro-3 : 6-di-*sec*.-butylpyrazine (IV, R = *sec*.-C₄H₉). The latter was characterised by hydrolysis to 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine (V, R = *sec*.-C₄H₉), identical with the preparation described in the preceding paper and with that described in Part II (*loc. cit.*).

EXPERIMENTAL.

2 : 5-Dimethylpyrazine Di-*N*-oxide.—A solution of 2 : 5-dimethylpyrazine (5.5 g.) in glacial acetic acid (20 c.c.) was treated with hydrogen peroxide solution (40 c.c.; 100-vol.) and maintained at 56° for 16 hours. The solution was evaporated to small bulk under reduced pressure, and the residue was cooled in ice-water and made alkaline with sodium hydroxide solution. The mixture was extracted with chloroform (10 × 25 c.c.), the extract dried (Na₂SO₄), and the solvent evaporated under reduced pressure. The solid residue was digested with boiling chloroform (25 c.c.), the mixture cooled, and the solid collected (filtrate A). Crystallisation from a large volume of chloroform gave 2 : 5-dimethylpyrazine di-*N*-oxide as needles (1.7 g.); it has no definite m. p., darkening profoundly at approximately 280°, and is not molten at 360°. The di-*N*-oxide is readily soluble in cold water but sparingly soluble in cold organic solvents. It is less soluble in 3*N*-sodium hydroxide solution than in water. It sublimes readily at 200°/0.5 mm. (Found: C, 51.3; H, 5.8. C₈H₈O₂N₂ requires C, 51.4; H, 5.7%).

2 : 5-Dimethylpyrazine *N*-Oxide.—The filtrate A and the mother liquors from the crystallisation of the di-*N*-oxide were combined, concentrated, and cooled, and some di-*N*-oxide was removed by filtration. The filtrate was evaporated to dryness and the solid residue (3.9 g.; m. p. 100°) was crystallised from benzene to give 2 : 5-dimethylpyrazine *N*-oxide as small colourless needles, m. p. 105–108°; it rapidly sublimes at 100°/0.001 mm. (Found: C, 58.0; H, 6.3. C₈H₈ON₂ requires C, 58.1; H, 6.45%). 2 : 5-Dimethylpyrazine *N*-oxide (0.6 g.) was heated with hydrogen peroxide solution (5 c.c.; 100-vol.) and glacial acetic acid (5 c.c.) for 18 hours at 56°. The reaction mixture was treated as described above to give 2 : 5-dimethylpyrazine di-*N*-oxide (0.5 g.), darkening at approximately 280° and not molten at 360° (Found: C, 51.5; H, 5.9%).

2-Chloro-3 : 6-dimethylpyrazine.—2 : 5-Dimethylpyrazine *N*-oxide (2.75 g.) was added in small portions to phosphoryl chloride (15 c.c.) with cooling and shaking. The mixture was cautiously warmed until solution was complete and the solution heated under reflux for 10 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on crushed ice. The mixture was neutralised with sodium carbonate and extracted with chloroform (6 × 25 c.c.), and the combined extracts were dried (Na₂SO₄). The chloroform was evaporated and the residual oil distilled under reduced pressure to give a main fraction, b. p. 75–80°/12 mm. (2.7 g.; 85%), which on redistillation yielded 2-chloro-3 : 6-dimethylpyrazine as a colourless oil, b. p. 77°/12 mm.; *n*_D²⁰ 1.5275 (Found: C, 50.8; H, 4.8; N, 19.4. Calc. for C₈H₈N₂Cl: C, 50.5; H, 4.9; N, 19.6%).

Hydrolysis of 2-chloro-3 : 6-dimethylpyrazine as described in the preceding paper gave a 50% yield of 2-hydroxy-3 : 6-dimethylpyrazine which after sublimation had m. p. 210–211°, undepressed on admixture with a specimen prepared *via* 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*).

2 : 5-Dichloro-3 : 6-dimethylpyrazine.—(a) 2 : 5-Dimethylpyrazine di-*N*-oxide (0.5 g.) was treated with phosphoryl chloride (2.5 c.c.) and heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue triturated with ice-water. The solid was collected and purified by sublimation to yield 2 : 5-dichloro-3 : 6-dimethylpyrazine (100 mg.), m. p. 70–72°, not depressed by the preparation described in the preceding paper (Found: C, 41.0; H, 3.5. Calc. for C₈H₆N₂Cl₂: C, 40.7; H, 3.4%).

(b) The di-*N*-oxide (0.5 g.) was refluxed for 1 hour with sulphuryl chloride (10 c.c.). The excess of reagent was removed by distillation to give 2 : 5-dichloro-3 : 6-dimethylpyrazine (90 mg.), m. p. 71–73°.

2 : 5-Di-*sec*.-butylpyrazine Di-*N*-oxide.—2 : 5-Di-*sec*.-butylpyrazine (4.2 g.) in glacial acetic acid (30 c.c.) and hydrogen peroxide solution (30 c.c.; 100-vol.) was heated at 56° for 17 hours. The solution

was evaporated to small bulk under reduced pressure, and the residue made alkaline with sodium hydroxide solution and extracted with chloroform (6 × 20 c.c.). The combined extracts were dried (K₂CO₃) and evaporated to dryness under reduced pressure. The residue was recrystallised from benzene-light petroleum (b. p. 40–60°) to give 2 : 5-di-*sec*.-butylpyrazine di-*N*-oxide as needles, m. p. 159–161° (yield 64%). 2 : 5-Di-*sec*.-butylpyrazine di-*N*-oxide is insoluble in water; it dissolves in 5*N*-hydrochloric acid and is precipitated on basification of the solution (Found: C, 64.2; H, 9.0. C₁₂H₂₀O₂N₂ requires C, 64.3; H, 8.9%).

2 : 5-Dichloro-3 : 6-di-*sec*.-butylpyrazine.—A mixture of the di-*N*-oxide (1.6 g.) and phosphoryl chloride (20 c.c.) was gently warmed and then heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured into ice-water. After neutralisation with sodium carbonate the solid was extracted with chloroform, and the dried (Na₂SO₄) extract

evaporated to yield an oil which solidified on cooling. The solid was purified by sublimation at 50°/0.5 mm., and the sublimate crystallised from aqueous ethanol to yield 2 : 5-dichloro-3 : 6-di-*sec.*-butylpyrazine (46% yield) as laminae, m. p. 59–61°, undepressed when mixed with the specimen described in the preceding paper (Found : C, 54.8; H, 6.9; N, 10.9. Calc. for $C_{12}H_{18}N_2Cl_2$: C, 55.2; H, 6.9; N, 10.7%).

2-Chloro-3 : 6-di-*sec.*-butylpyrazine.—The mother liquors from the crystallisation of 2 : 5-di-*sec.*-butylpyrazine di-*N*-oxide were evaporated. The viscous liquid (1.0 g.), which would not solidify, was heated under reflux with phosphoryl chloride (10 c.c.) for 30 minutes and the reaction mixture worked up in the usual manner to give 2-chloro-3 : 6-di-*sec.*-butylpyrazine (0.6 g.) as a colourless oil, b. p. 118–120°/14 mm.; n_D^{20} 1.5037 (Found : N, 12.1. Calc. for $C_{12}H_{18}N_2Cl$: N, 12.4%). Treatment of the chloro-compound (0.4 g.) with potassium hydroxide using the conditions described in the preceding paper gave 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (0.15 g.) as small needles which after sublimation had m. p. and mixed m. p. 121–123°.

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[Received, November 27th, 1946.]

223. Nitration in Sulphuric Acid. Part V. Nitration of 2 : 4-Dinitrotoluene in a Two-phase System.

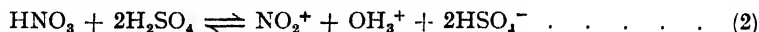
By G. M. BENNETT, J. C. D. BRAND, D. M. JAMES, T. G. SAUNDERS, and GWYN WILLIAMS.

The results of a series of experiments on the rate of nitration of dinitrotoluene in a two-phase system under various conditions are discussed in the light of the study of nitration in homogeneous sulphuric acid solution (Part IV, this vol. p. 474), but a complete analysis of the results is not possible owing to the lack of data concerning the concentrations in the two phases.

The rate of nitration for any one concentration of nitric acid is approximately proportional to the molar excess of sulphuric acid over water present.

Owing to the higher proportion of nitric acid and lower proportion of sulphuric acid present in comparison with the experiments in homogeneous solution, and also to solubility effects, there is no optimum composition of the acid mixture giving a maximum rate of nitration such as occurs with 92% sulphuric acid in homogeneous nitration. Consistently with this the influence of added bisulphates and nitrous acid is in all cases to depress the rate of reaction.

PART IV (*loc. cit.*) of this series described a study of the kinetics of nitration of 2 : 4-dinitrotoluene in homogeneous solution in sulphuric acid, with small concentrations of nitric acid and nitro-compound. The influence of water upon the rate of nitration was shown to be due to the production of bisulphate ion (equation 1), which exerts a dual influence, assisting nitration by increasing the proton-accepting quality of the medium and hindering nitration by its effect upon the extent to which nitric acid is converted into the nitronium ion NO_2^+ (equation 2). This ion is the effective nitrating agent (Part I, *J.*, 1946, 869).



In actual practice, however, the conversion of dinitrotoluene (DNT) into trinitrotoluene (TNT), whether on the laboratory or on the industrial scale, is carried out with larger proportions of nitric acid and with sufficient organic material to produce a two-phase system. In this paper we present the results of laboratory experiments on the two-phase nitration of DNT, designed to show whether the influence of water upon the rate of nitration in a two-phase system is consistent with the conclusions derived from the experiments with homogeneous systems, and, in particular, to ascertain whether added bisulphate ion influences the rate of the two-phase nitration in a predictable manner. The results here described will be confined to those of importance for these two purposes: a more extensive account of the two-phase experiments, with full experimental details, will be published elsewhere.

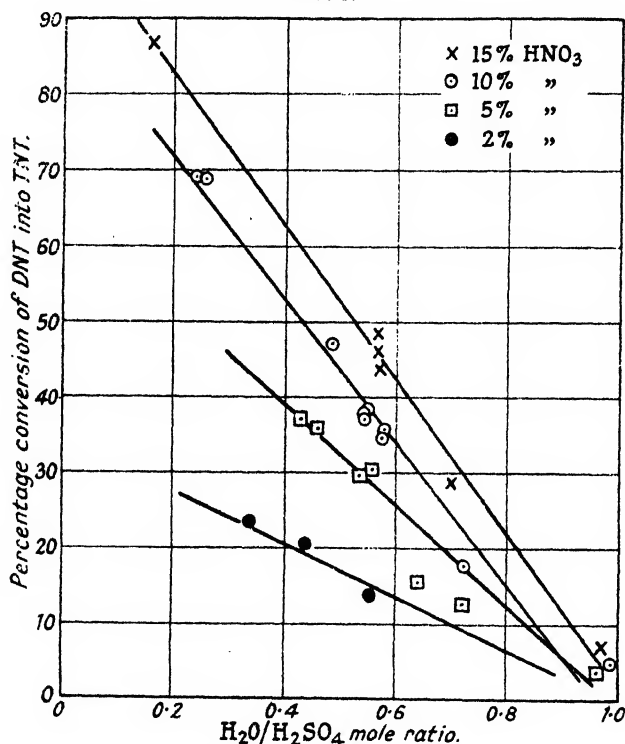
Method of Experiment.—In each nitration chosen quantities of reagents were vigorously stirred together at a specified temperature (usually 100°) for a certain time (usually 60 mins.), the reaction was stopped by pouring into water, and the composition of the organic products found, after washing and drying, by measurement of density with a pyknometer and by reference to a density-composition curve. The material subjected to nitration was usually a 50% dinitrotoluene-trinitrotoluene mixture in order to make the experiment similar in conditions to those found in one of the vessels of a nitrating plant where nitration is proceeding vigorously.

To determine strictly comparable rates of reaction would require the measurement of instantaneous initial velocities of the process, but the experimental errors would be large for

short times of reaction so that a compromise was necessary and the nitrations were continued for times sufficient to give changes large enough for accurate determination. A consideration of the various experimental errors shows that an observed change of 1% in the proportion of TNT present may be regarded as significant, but the corresponding calculated percentage conversion will be of the order of 2%.

Sulphuric Acid-Water Ratio.—The criteria we have used in examining the process are the $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ and the HNO_3/DNT molar ratios. Fig. 1 summarises the results obtained at 100° with widely varying $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ratios for four different values of the HNO_3/DNT ratio, and shows clearly that nitration becomes negligible when the water/sulphuric acid ratio approaches unity. This is reminiscent of the nitration threshold found by Hetherington and Masson (*J.*, 1933, 105) for the nitration of nitrobenzene at 35° , but the latter substance has a much higher speed of nitration and, in presence of large amounts of nitric acid, its nitration continued to

FIG. 1.



Extent of nitration in 1 hour at 100° of 50% DNT in TNT mixture with 2.43 wts. of mixed acids of various compositions.

points somewhat beyond the 1 : 1 ratio of water to sulphuric acid. The results of our velocity measurements for the nitration of dinitrotoluene in homogeneous solution show values falling towards zero in the region of a $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ mole ratio of 0.87, and although this agrees approximately with the indications of Fig. 1 there appears to be a small but real discrepancy since appreciable nitration was found in two-phase experiments for acids of ratio 1.0. The explanation of this may lie in the slight change of composition of the acid mixture in consequence of the partition of water and acids between the two phases. Complete data on this point are not available, but some unpublished experiments by Mr. S. E. Napier, made to study the compositions of the two phases in such nitrations, showed that the aqueous acid present in the organic phase, amounting to 5–10% of that phase, always showed a $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ratio much higher than that of the acid phase in equilibrium with it. This must result in the effective $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ molar ratio in two-phase nitrations being somewhat lower than that of the acid mixture as prepared and analysed before the experiment, and may well account for the discrepancy observed.

Fig. 1 shows that rates of nitration for each concentration of nitric acid fall in an approximately linear manner towards the point when $\text{H}_2\text{O}/\text{H}_2\text{SO}_4 = 1$, and this means that the rates are nearly proportional to $1 - \text{H}_2\text{O}/\text{H}_2\text{SO}_4$ or $(\text{H}_2\text{SO}_4 - \text{H}_2\text{O})/\text{H}_2\text{SO}_4$, i.e., nearly proportional to the fraction of sulphuric acid which is in molar excess of the water present. This is consistent with our view that nitration must depend on there being a molecular excess of sulphuric acid over the water present in the nitrating mixture, because the reaction (1) is complete, and it is only the excess of sulphuric acid which converts nitric acid into the active nitrating species NO_2^+ on which the reaction depends.

A detailed analysis of the results of these two-phase experiments in terms of the velocities of reaction determined in homogeneous sulphuric acid solution is, however, not at present possible because the available data as to the exact compositions of the two phases are far too fragmentary.

A remarkable regularity was observed in the course of some experiments carried out by Messrs. J. C. Dine and D. Fysh directed to answering the practical question "what is the necessary composition of mixed acid to give a specified extent of nitration?" It was found that for various concentrations of nitric acid (of 5% and upward when working at 100°) the required rate of nitration was obtained when the water mole-fraction had a certain value. Moreover, this was found to hold at three different temperatures, a necessary minimum concentration of nitric acid and a prescribed water mole-fraction being specified for each temperature.

A partial explanation of this result is again suggested by our theory when the concentrations of nitronium ion present in these acid mixtures are considered. Calculation from the ionic equilibria, using the constants determined in our study of kinetics in homogeneous sulphuric acid solution (Part IV, *loc. cit.*), shows that the acids giving the required rate of nitration have approximately constant concentrations of NO_2^+ ion. The data for six such acids found to give a prescribed rate of 16.5% conversion of DNT in 30 minutes at 100° are shown in the table

Composition of nitrating acids giving a specified rate of nitration at 100°.

Acid No.	Wt., %.			Mole-fractions.			Calculated moles of NO_2^+ /l.
	H_2SO_4 .	HNO_3 .	H_2O .	H_2SO_4 .	HNO_3 .	H_2O .	
1	75.0	15.0	10.0	0.489	0.152	0.359	0.60
2	80.6	9.85	9.6	0.543	0.103	0.354	0.72
3	85.4	5.06	9.5	0.590	0.054	0.356	0.62
4	87.3	3.94	8.8	0.618	0.043	0.338	0.64
5	87.5	3.71	8.75	0.621	0.041	0.338	0.61
6	93.6	2.0	4.4	0.776	0.026	0.198	0.58

above. The experimental measurements of Chédin (*Mem. des Services chimiques de l'Etat*, 1944, 31, 113), interpreted according to our views, give results of the same order and equally consistent except for acid No. 6. Such acids might be expected to have equal nitrating powers. This leaves out of account, however, the two-phase nature of the system, and the fact that the concentrations in the acid phase, where nitration takes place, must differ slightly from those in the nitrating acid selected.

When a wide range of nitration data are re-examined in relation to the water mole-fraction in the acid used it appears from Fig. 2, in which the extent of nitration is plotted against the water mole-fraction, that with acids of 5% nitric acid and upwards the rate of nitration varies in a linear manner with varying water mole-fraction, independently of wide variations in the concentration of nitric acid present.

It may be pointed out that acids of the same water mole-fraction are acids of nearly equal water/sulphuric acid ratios since the mole-fraction of sulphuric acid in them does not vary much. In fact, if the nitric acid present is increased while the water mole-fraction is kept constant, a slightly lower $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ratio must result and the relationship shown in Fig. 2 may arise from a compensation in the ionisation equilibrium between a somewhat diminished proportion of free sulphuric acid and the increased amount of nitric acid present.

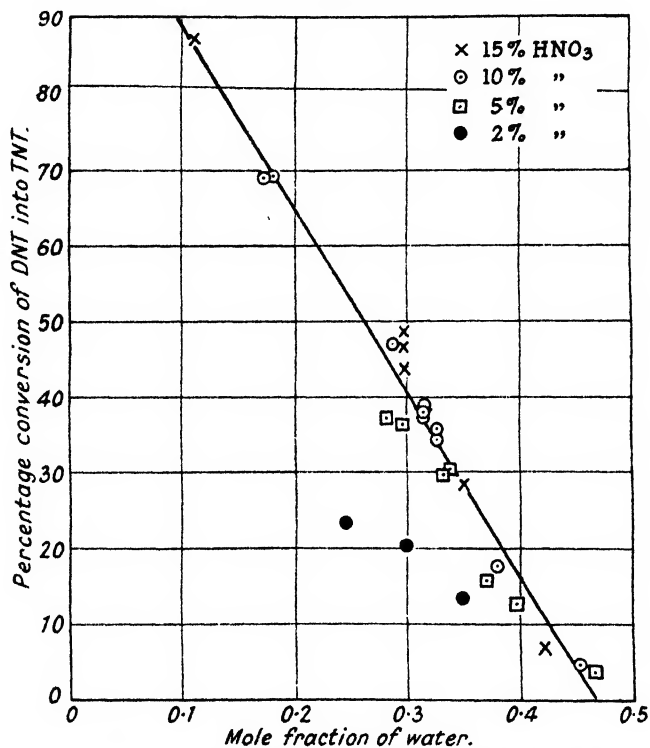
If, on the other hand, we consider the trend of the results of two-phase nitrations in acids of diminishing water content, we find that the nitration rates (using nitrating acids containing 5 or 10% HNO_3) increase steadily as the mole-fraction of water is reduced to zero and show no sign of a maximum for a nitrating acid composed of nitric acid and any aqueous sulphuric acid, comparable with the sharp maximum in homogeneous solutions at 92% H_2SO_4 ($\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ molar ratio = 0.48). There are two reasons which may account for this difference:

(a) In two-phase experiments with dinitrotoluene the nitration takes place in the acid

phase. Nitration in the organic phase is negligible, as shown by Mr. W. W. Jones and Mr. A. E. Flood (unpublished observations; compare Hetherington and Masson, *loc. cit.*, who state that no nitration occurs in the nitrobenzene phase, and Lewis and Suen, *Ind. Eng. Chem.*, 1940, **32**, 1095, who found the rate of nitration of benzene to be 5–10 times as fast in the acid phase as in the organic phase). The solubility of dinitrotoluene in the acid phase increases with diminishing water content, and this must at least tend to move the optimum composition for nitration in the direction of acids of lower water content (compare D. I. James, *J.*, 1935, 785).

(b) The occurrence of a medium giving a maximum rate for homogeneous nitration depends on the existence of a range of nitrating acids in which an increase in water content accelerates nitration, and this is due to the nearly complete conversion of water and nitric acid into ionic forms by the sulphuric acid in this range. The rising proportion of water therefore increases the concentration of HSO_4^- ion in this region much faster than it diminishes that of the NO_2^+

FIG. 2.



Extent of nitration in 1 hour at 100° of 50% DNT in TNT mixture with 2.43 wts. of mixed acids of various compositions.

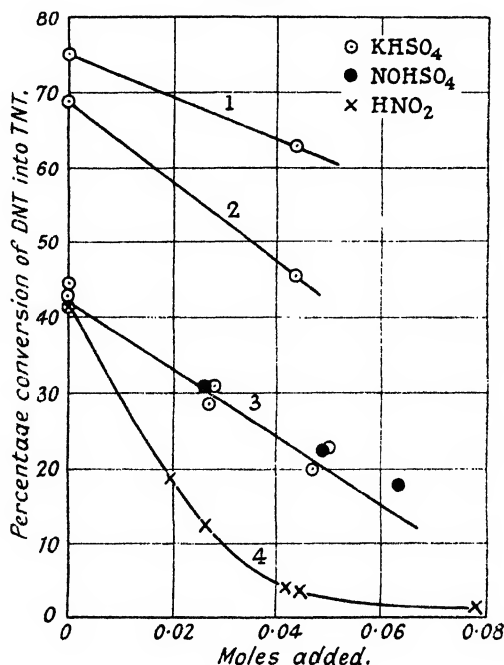
ion. This can only occur, however, when sulphuric acid is present in sufficient molecular excess over both water and nitric acid. In a typical two-phase experiment the nitrating acid was of composition 84.4% H_2SO_4 , 9.9% HNO_3 , 5.7% H_2O (nitric acid in 93.7% sulphuric acid) and the actual quantities in reaction were: dinitrotoluene 0.0384, sulphuric acid 0.293, nitric acid 0.0538, water 0.108 mole. In this mixture sulphuric acid is in 1.8-fold excess over the nitric acid plus water, as compared with a 4-fold excess in our homogeneous nitration in 96% sulphuric acid. It is readily shown by calculation of the ionic equilibria in these mixtures (discussed in Parts I and IV of this series) that with 5 or 10% of nitric acid present the conversion of the nitric acid into the cationic form NO_2^+ does not approach completeness with any sulphuric acid–water mixture. An examination of the curves from the observations of Chédin (*loc. cit.*) also leads to the same conclusion.

This view is supported by the effect produced on the rate of nitration by the addition of bisulphates.

Effect of Bisulphates and Nitrous Acid.—In Part IV it was shown that the effect of bisulphate

ions in homogeneous nitrations was to accelerate the reaction in the region between the optimum concentration and 100% sulphuric acid but to retard it in acid-water mixtures of less than 92% sulphuric acid. According to our view, the two-phase nitrating mixtures are all effectively analogous to the latter range of media for homogenous nitration, and this requires that bisulphates should always retard the two-phase process. This question has been examined experimentally, for two-phase nitrations with a mixed acid containing 10% of nitric acid, by observing the effect of adding (a) potassium bisulphate, (b) nitrosyl bisulphate, and (c) nitrous acid. The last of these reacts reversibly according to the equation $\text{HNO}_2 + 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^-$, so that one mole of nitrous acid produces two moles of bisulphate ion and one mole of oxonium ion all capable of affecting the nitric acid ionisation equilibrium.

FIG. 3.



Effects of added substances on extent of nitration at 100°.

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|----------|--|------------------------|----------------------------|
| Curve 1. | 89.1% H_2SO_4 : $\text{H}_2\text{O}/\text{H}_2\text{SO}_4 = 0.072$. | Nitration for 30 mins. | } $\text{HNO}_3 = 9.8\%$. |
| 2. | 86.2% H_2SO_4 : $\text{H}_2\text{O}/\text{H}_2\text{SO}_4 = 0.245$. | Nitration for 60 mins. | |
| 3 and 4. | 81.8% H_2SO_4 : $\text{H}_2\text{O}/\text{H}_2\text{SO}_4 = 0.563$. | Nitration for 60 mins. | |

The results of these experiments are shown in Fig. 3. A retardation of the reaction is apparent in all cases. The large retarding effect of bisulphate, shown in the upper two curves, is specially noteworthy since the $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ratios for these acids were 0.072 and 0.245, corresponding to points well on the acid side of the optimum velocity point in homogeneous nitrations ($\text{H}_2\text{O}/\text{H}_2\text{SO}_4 = 0.48$). This confirms the supposition made above [p. 1188, (b)] that, in two-phase nitration, the proportion of nitric acid present is usually too high for its conversion into nitronium ion to be nearly complete.

In this connection it is noteworthy that the nitration of benzoic acid and other substances by means of potassium nitrate and concentrated sulphuric acid (Houben, "Methoden der Organischen Chemie", 3rd edn., 1941, iv, 195) involves essentially homogeneous conditions and that here the reaction is facilitated by the potassium bisulphate formed in solution.

The effects of potassium and nitrosyl bisulphate are not quite equivalent, but the discrepancy is accounted for when allowance is made for the incompleteness of the ionisation reaction of nitrous acid: the substance is 90% ionised in such solutions according to the estimate of Hantzsch and Berger (*Z. anorg. Chem.*, 1930, 190, 321).

The effect of nitrous acid in depressing the speed of nitration is seen to be more than twice

that of potassium bisulphate, as was to be expected, but here again the result is modified by the reversal of the ionisation equilibrium.

The influence of nitrous acid upon two-phase nitration has made itself felt in another way. If the initial nitrating agent contains too high a proportion of water, nitration stops before the whole of the available reacting material has been consumed. Such an effect, which is similar to the nitration threshold of Hetherington and Masson for nitrobenzene (compare p. 1186), is a natural consequence of the accumulation of water liberated during nitration with a consequent increase of the $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ratio to a point where the speed of nitration becomes negligible. But the arrest in the nitration of DNT actually occurs at an earlier stage, because the oxidation processes accompanying the nitration (see Part IV, *loc. cit.*) produce nitrous acid, the retarding action of which is added to that of the water in bringing the reaction to a standstill.

The authors express their thanks to Professor W. E. Garner, F.R.S., in whose laboratory this work was carried out, and to the Director-General of Scientific Research (Defence) for permission to publish.

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224. β -Cycloylpropionitriles. Part I. A General Synthesis and Conversion into Pyrrole Dyes.

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Cyclyl β -dialkylaminoethyl ketone hydrochlorides, readily obtained by the Mannich reaction, are converted to β -cycloylpropionitriles by refluxing with aqueous potassium cyanide. The nitriles on hydrolysis yield β -cycloylpropionic acids some of which are not otherwise readily available. β -Benzoylpropionitrile readily absorbs hydrogen chloride to give a crystalline chloroimide salt which on treatment with alcohol gives an alkyl β -benzoylpropimino-ether hydrochloride. The latter, also formed by the conventional method, gives with hot alcoholic ethyl orthoformate, red 3:3'-pyrromethin and with β -ethoxyacetaldehyde acetal, a blue 3:3'-pyrrotrimethin dye.

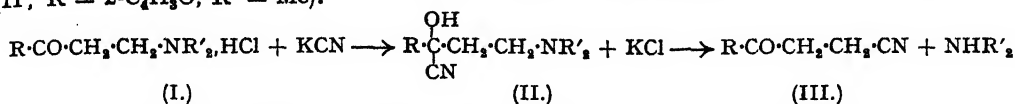
THE preparation of β -cycloylpropionic acids is normally achieved by a Friedel-Crafts condensation of an unsaturated carbocycle or heterocycle with succinic anhydride. This method gives positive results with most suitable carbocyclic and stable heterocyclic compounds. The same acids can also be prepared from the cyclyl bromomethyl ketone by condensation with ethyl sodiomalonate followed by hydrolysis and decarboxylation. Both of these methods fail, however, when the cyclic component is relatively unstable. Thus furan or 2-bromoacetylfuran gave only tars when submitted to either of the above processes. Since β -2-furoylpropionic acid was required, an alternative method of preparation was sought.

One method would be by the hydrolysis of β -2-furoylpropionitrile if such a compound were readily available. No general method for the preparation of β -cycloylpropionitriles has been developed, although one such nitrile, β -benzoylpropionitrile (β -cyanopropiophenone) was prepared by Allen, Gilbert, and Young (*J. Org. Chem.*, 1937, 2, 227) by the addition of hydrogen cyanide to phenyl vinyl ketone.

It is well known (Mannich and Hönig, *Arch. Pharm.*, 1927, 265, 598) that cyclyl β -dialkylaminoethyl ketones vary in their stability and that many of them, on steam distillation, lose dialkylamine to give cyclyl vinyl ketones. It is also known (Reichert and Posemann, *ibid.*, 1937, 275, 67) that Mannich salts react with sodionitromethane to give γ -nitrobutyrophenones. It appeared fruitful, therefore, to investigate the action of alkali cyanides on Mannich salts, since such alkalis should release the Mannich bases, and under certain conditions the latter, by loss of dialkylamine followed by hydrogen cyanide addition, might be converted into the desired nitriles.

It has been reported (Mannich and Braun, *Ber.*, 1920, 53, 1874) that the Mannich salt obtained from cyclohexanone on treatment with aqueous potassium cyanide yields a cyanohydrin of the Mannich base. The β -dialkylaminopropiophenone hydrochlorides (I; R = Ph) which were chosen for model experiments also gave oils on the addition of aqueous potassium cyanide. These are believed to be the cyanohydrins (II; R = Ph) but they readily decomposed on attempted distillation and were not analysed. The product from 2-furyl β -dimethylamino ethyl ketone hydrochloride (I; R = 2-C₄H₃O) and cold aqueous potassium cyanide, however,

was obtained crystalline and found to be 2-furyl β -dimethylaminoethyl ketone cyanohydrin (II; R = 2-C₄H₃O, R' = Me).



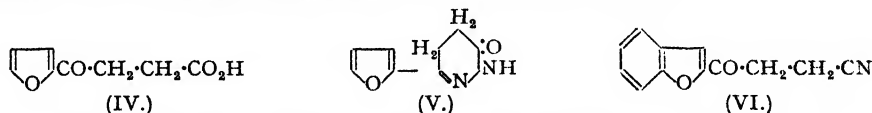
The decomposition of (II; R = Ph), with or without its isolation, was readily brought about by short heating under reflux in water, preferably in the presence of excess alkali cyanide. Dialkylamine was evolved, and β -benzoylpropionitrile formed in reasonably good yield. The yield and the state of purity of the crude product, as well as the optimal reaction time, depended primarily on the concentration of the aqueous cyanide. The greater the dilution the purer was the product, and up to a point the higher the yield. Too great a dilution lowered the yield, owing to the solubility of the nitrile in water. Replacement of water as solvent by aqueous alcohol, and other combinations, always gave lower yields.

The application of this method to other salts (I; R = aryl, or 2-thienyl) gave similar yields of nitrile. β -2-Furoylpropionitrile is much more soluble than the other nitriles and must be extracted from the reaction mixture. 2-Benzfuryl β -cyanoethyl ketone (VI) was also obtained by this method. The reaction appears to be fairly general and the only exception amongst the salts used involved 3-nitro- β -dimethylaminopropiophenone hydrochloride. This salt, the base of which is known to be very unstable, readily releasing amine and formaldehyde (Mannich and Dannehl, *Arch. Pharm.*, 1938, 276, 206), gave only resins with potassium cyanide. 1-Naphthyl β -dimethylaminoethyl ketone hydrochloride, which decomposed rapidly on heating in aqueous solution, gave the expected nitrile only when a large excess of cyanide was present.

The reaction applied to *p*-chloro- β -dimethylaminopropiophenone hydrochloride gave only a 16.5% yield of the required nitrile and a second solid, analysis of which indicated the empirical formula C₁₈H₁₅O₂NCl₂. It formed a monophenylhydrazone and was decomposed to an oil by boiling 18% hydrochloric acid. The simplest substance of this composition, *viz.*, Cl·C₆H₄·CO·CH₂·CH₂·C(NH)·CH₂·CH·CO·C₆H₄Cl, would be formed by addition of the intermediate *p*-chlorophenyl vinyl ketone to the *p*-chlorobenzoylpropionitrile, giving 4-imino-1 : 7-diketo-1 : 7-di-*p*-chlorophenylhept-2-ene.

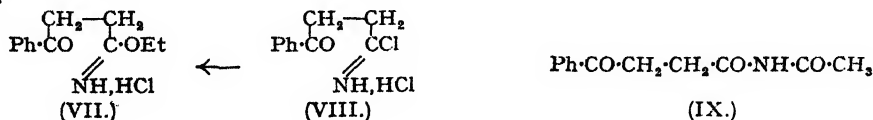
This method of preparation of the nitriles appears to apply only where R' is alkyl. Such Mannich salts obtained by the substitution of dialkylamines by piperidine or morpholine do not decompose under the conditions employed here. Similarly, Mannich salts from cyclic ketones or propiophenone gave only oils or resins on similar treatment.

In all cases the nitrile was readily hydrolysed to the β -cycloylpropionic acid (cf. Allen *et al.*, *loc. cit.*). β -2-Furoylpropionic acid (IV) resembles β -benzoylpropionic acid in its melting point and physical appearance. It was characterised by its ethyl ester and its conversion into 3-keto-6-(2'-furyl)-2 : 3 : 4 : 5-tetrahydropyridazine (V) by hydrazine hydrate.



On treating an alcoholic solution of β -benzoylpropionitrile with hydrogen chloride, ethyl β -benzoylpropimino-ether hydrochloride (VII) was obtained, the base of which is crystalline but not very stable; (VII) was also obtained by treating the nitrile with hydrogen chloride in dry benzene and dissolving the resulting, crystalline chloroimide salt (VIII) in ethyl alcohol. The chloroimide fumed strongly in air, slowly releasing hydrogen chloride to give the original nitrile. It was decomposed by water to give chiefly the original nitrile together with some β -benzoylpropionamide.

On warming (VII) with 18% hydrochloric acid, ethyl β -benzoylpropionate was formed in quantitative yield, whilst its base, on heating with acetic anhydride, gave the expected N- β -benzoylpropionylacetamide (IX). The corresponding imino-ether salts from β -4-methoxybenzoylpropionitrile and β -4-hydroxybenzoylpropionitrile are very sensitive to moisture, and on dissolving in 99% alcohol were converted into β -4-methoxy- and β -4-hydroxybenzoylpropionamides.



ethyl alcohol. A sample was obtained as glistening plates, m. p. 192°, from ethyl alcohol, in which it is sparingly soluble (Found: N, 6.2; Cl, 15.2. $C_{11}H_{11}O_2NCl$ requires N, 6.1; Cl, 15.45%).

4-Bromo- β -dimethylaminopropiophenone Hydrochloride (I; R = 4-BrC₆H₄).—*p*-Bromoacetophenone (25 g.), dimethylamine hydrochloride (12 g.), paraformaldehyde (4.5 g.), concentrated hydrochloric acid (0.5 c.c.), and ethyl alcohol (30 c.c.) were refluxed together for 2 hours, then chilled, and acetone (50 c.c.) added; the salt (17.9 g.; 49%) crystallised, and formed jagged needles, m. p. 196°, from ethyl alcohol (Found: N, 4.7. $C_{11}H_{11}ONClBr$ requires N, 4.8%).

2-Benzfuryl β -Dimethylaminoethyl Ketone Hydrochloride (I; R = 2-benzfuryl).—2-Acetylbenzofuran (34 g.) (Stoermer and Schäfer, *Ber.*, 1903, **36**, 2863), dimethylamine hydrochloride (17.3 g.), paraformaldehyde (7.2 g.), and ethyl alcohol (100 c.c.) were refluxed together for 2 hours. The clear solution was concentrated to half its volume, acetone (200 c.c.) added, and the mixture chilled. The crystals (21 g.; 39%) were washed with acetone and obtained as tiny needle rosettes (Found: N, 5.15; Cl, 13.5. $C_{15}H_{15}O_2NCl$ requires N, 5.5; Cl, 14.0%), m. p. 188°, from ethyl alcohol. The filtrates gave unchanged acetylbenzofuran (16.5 g.) on dilution with water.

α -Dimethylaminomethylpropiofenone Hydrochloride.—Propiophenone (134 g.), dimethylamine hydrochloride (106 g.), paraformaldehyde (40 g.), concentrated hydrochloric acid (2 c.c.) and ethyl alcohol (160 c.c.) were heated under reflux for 2 hours. After cooling, ether was added to precipitate an oil, which solidified on shaking (184 g.; 81%). It formed tiny needles, m. p. 142.5°, from ethyl alcohol-ether (Found: N, 6.35. $C_{11}H_{11}ONCl$ requires N, 6.15%).

β -Benzoylpropionitrile (III; R = Ph).—(a) β -Dimethylaminopropiophenone hydrochloride (213.5 g.; 1 mol.) (*Org. Synth.*, **23**, 30) and potassium cyanide (130 g.; 2 mols.) were placed in a flask and boiling water (2600 c.c.) added rapidly. The whole, consisting of an aqueous and an oily layer, was refluxed for 30 minutes. Part of the dimethylamine distilled and was collected in dilute hydrochloric acid. On chilling, the oil crystallised, and crystals formed from the aqueous layer. The nitrile (67% yield) formed almost colourless blades, m. p. 76°, from benzene-light petroleum (Found: C, 75.2; H, 5.85; N, 8.6. Calc. for C₁₀H₉ON: C, 75.5; H, 5.65; N, 8.8%). Allen *et al.* (*loc. cit.*) give m. p. 76° from ethyl alcohol.

(b) Crude β -diethylaminopropiophenone hydrochloride contaminated with diethylamine hydrochloride (900 g.) was obtained by refluxing for 2 hours a mixture of acetophenone (422 g.), diethylamine hydrochloride (500 g.), paraformaldehyde (138 g.), concentrated hydrochloric acid (7 c.c.), and ethyl alcohol (280 c.c.) and adding dry ether to the cooled reaction mixture until no more solid precipitated. The crude salt (24.1 g.), potassium cyanide (13 g.), and boiling water (520 c.c.) were refluxed for 20 minutes, and the nitrile, m. p. 76°, isolated and purified as under (a). The yield of nitrile was 48% based on the diethylamine hydrochloride.

β -*p*-Toluyloxypropionitrile (II; R = *p*-MeC₆H₄).— β -Dimethylamino-4-methylpropiophenone hydrochloride (22.7 g.; 0.1 mol.), potassium cyanide (13.0 g.; 0.2 mol.), and boiling water (520 c.c.) were refluxed for 20 minutes. The crystalline nitrile (9.0 g.; 52%) obtained on chilling formed glossy needles, m. p. 76°, from ethyl alcohol (Found: N, 8.15. $C_{11}H_{11}ON$ requires N, 8.2%).

β -*p*-Chlorobenzoyloxypropionitrile (II, R = *p*-ClC₆H₄).— β -Chloro- β -dimethylaminopropiophenone hydrochloride (124 g.) (Dhont and Wibaut, *Rec. Trav. chim.*, 1944, **63**, 81), potassium cyanide (65 g.), and boiling water (2600 c.c.) were refluxed together for 30 minutes. On chilling, the oil solidified. It was washed, and dissolved in ethyl alcohol. On cooling, the nitrile (16 g., 16.5%) crystallised. It formed flat, colourless needles, m. p. 72.5°, from ethyl alcohol (Found: N, 7.35. $C_{10}H_8ONCl$ requires N, 7.25%). The primary filtrate on prolonged standing gave a second solid (18.0 g.) which was obtained as fine white needles, m. p. 115°, from ethyl alcohol (Found: C, 63.35; H, 4.3; N, 3.95; Cl, 19.45. $C_{10}H_8O_2NCl_2$ requires C, 63.35; H, 4.15; N, 3.9; Cl, 19.7%). Its monophenylhydrazones formed pale yellow, feathery needles, m. p. 146–148°, from alcohol (Found: N, 8.95. $C_{28}H_{21}ON_3Cl_2$ requires N, 9.35%). The filtrates from the second crystallisation, on concentration, gave a further crop of nitrile (14.4 g.), m. p. 72.5°, so the total yield of the required nitrile was 31.5%. It was readily hydrolysed to β -*p*-chlorobenzoylpropionic acid, m. p. 134° (Skraup and Schwamberger, *Annalen*, 1928, **462**, 135, give m. p. 134°).

β -*p*-Bromobenzoyloxypropionitrile (II; R = *p*-BrC₆H₄).— β -Bromo- β -dimethylaminopropiophenone hydrochloride (14.6 g.), potassium cyanide (6.5 g.), and boiling water (130 c.c.) were refluxed for 20 minutes. On chilling, the oil crystallised. The nitrile (7.2 g.; 62.5%) formed tiny needles, m. p. 81°, from ethyl alcohol (Found: N, 5.65. $C_{10}H_8ONBr$ requires N, 5.9%).

β -*p*-Bromobenzoylpropionic Acid.—The nitrile (1 g.) was refluxed for 1 hour with concentrated hydrochloric acid (10 c.c.), and the acid which crystallised on cooling was dissolved in aqueous sodium carbonate, and the solution filtered and acidified. The acid formed colourless needles, m. p. 148°, from water (Found: Br, 31.2. $C_{10}H_8O_3Br$ requires Br, 31.1%).

β -3-Hydroxybenzoyloxypropionitrile (III; R = 3-OH-C₆H₄).— β -Dimethylamino-3-hydroxypropiophenone hydrochloride (41 g.), potassium cyanide (23.2 g.), and boiling water (900 c.c.) were refluxed for 30 minutes. The chilled liquor gave on acidification with acetic acid an oil which slowly solidified. It crystallised as needles, m. p. 98°, from aqueous alcohol (Found: N, 8.2. $C_{10}H_9O_2N$ requires N, 8.0%). The acid, obtained by refluxing the nitrile (2 g.) with 18% hydrochloric acid (20 c.c.), for 1 hour, formed irregular plates, m. p. 146.5°, from water (Found: C, 61.75; H, 5.0. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.15%).

β -4-Hydroxybenzoyloxypropionitrile (III; R = 4-OH-C₆H₄).—Prepared as for the 3-isomer, this nitrile was precipitated as a crystalline solid on the addition of acetic acid to the reaction mixture. It was obtained as colourless, flat needles, m. p. 162°, from a little ethyl alcohol in 59% yield (Found: C, 68.35; H, 5.35; N, 7.95. $C_{10}H_9O_2N$ requires C, 68.55; H, 5.15; N, 8.0%). The acid formed colourless needles, m. p. 157°, from hot water. Fieser *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2966) give m. p. 154–156° (Found: C, 61.55; H, 5.05. Calc. for C₁₀H₁₀O₄: C, 61.85; H, 5.15%).

β -3-Methoxybenzoyloxypropionitrile (III; R = 3-MeO-C₆H₄).— β -Dimethylamino-3-methoxypropiophenone hydrochloride (12.2 g.; 0.05 mol.), potassium cyanide (13 g.; 0.2 mol.), and boiling water (520 c.c.) were refluxed for 10 minutes. On chilling, the oil crystallised. It formed colourless needles, m. p. 54°.

in 73% yield from methyl alcohol by repeated concentration of the filtrates (Found: N, 7.2. $C_{11}H_{11}O_2N$ requires N, 7.4%). The acid was obtained on hydrolysis of the nitrile with 18% hydrochloric acid as colourless needles, m. p. 108°, from water (Found: C, 63.2; H, 5.95. $C_{11}H_{11}O_4$ requires C, 63.45; H, 5.75%).

β -4-Methoxybenzoylpropionitrile (III; R = 4-MeO-C₆H₄).— β -Dimethylamino-4-methoxypropionophenone hydrochloride (24.35 g.; 0.1 mol.), obtained in 86% yield by the method given for the unsubstituted product (*Org. Synth.*, 23, 31) (cf. Mannich and Lammering, *Ber.*, 1922, 55, 3510), potassium cyanide (13.0 g.; 0.2 mol.), and boiling water (520 c.c.) were refluxed for 20 minutes and chilled. The nitrile was obtained as glassy needles, m. p. 95°, from ethyl alcohol in 71% yield (Found: C, 69.6; H, 5.7; N, 7.65. $C_{11}H_{11}O_2N$ requires C, 69.85; H, 5.8; N, 7.4%). The acid had m. p. 144°, alone, and mixed with a specimen prepared from anisole and succinic anhydride (Poppenberg, *Ber.*, 1901, 34, 5257).

β -3:4-Dimethoxybenzoylpropionitrile (II, R = (MeO)₂C₆H₃).— β -Dimethylamino-3:4-dimethoxypropionophenone hydrochloride (21 g.) (Mannich and Lammering, *loc. cit.*), potassium cyanide (10 g.), and boiling water (400 c.c.) were refluxed for 20 minutes. The nitrile (13.3 g., 85%) was obtained as glassy needles, m. p. 118°, from ethyl alcohol (Found: N, 6.5. $C_{12}H_{13}O_4N$ requires N, 6.4%).

β -1-Naphthoylpropionitrile (III; R = 1-C₁₀H₇).—1-Naphthyl β -dimethylaminoethyl ketone hydrochloride (5 g.; 1 mol.), potassium cyanide (5.0 g.; 4 mols.), and boiling water (200 c.c.) were refluxed for 30 minutes. The solid obtained on chilling (1.7 g.; 42.5%) formed tiny needle rosettes, m. p. 113–114°, from methyl alcohol (Found: C, 79.8; H, 5.3; N, 6.9. $C_{14}H_{11}ON$ requires C, 80.4; H, 5.25; N, 6.7%).

β -2-Naphthoylpropionitrile (III; R = 2-C₁₀H₇).—2-Naphthyl β -dimethylaminoethyl ketone hydrochloride (50 g.) (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, 64, 431), potassium cyanide (50 g.), and boiling water (1 l.) were refluxed for 30 minutes. The nitrile (15.1 g., 38%), obtained on chilling, formed clusters of yellow needles, m. p. 114°, from ethyl alcohol (Found: N, 6.65%).

2-Furyl β -Dimethylaminoethyl Ketone Cyanohydrin (II; R = 2-C₄H₃O, R' = Me).—2-Furyl β -dimethylaminoethyl ketone hydrochloride (8.15 g.; 0.04 mol.) (Levy and Nisbet, *J.*, 1938, 1055) was dissolved in cold water (5 c.c.), and a solution of potassium cyanide (5.2 g.; 0.08 mol.) in water (10 c.c.) added. Colourless crystals of the cyanohydrin separated. It formed colourless needles, m. p. 45°, from ligroin (Found: C, 62.2; H, 7.2; N, 14.3. $C_{10}H_{11}O_2N_2$ requires C, 62.0; H, 7.2; N, 14.45%).

β -2-Furoylpropionitrile (III; R = 2-C₄H₃O).—2-Furyl β -dimethylaminoethyl ketone hydrochloride (81.5 g.; 0.4 mol.), potassium cyanide (52 g.; 0.8 mol.), and boiling water (2850 c.c.) were refluxed for 30 minutes, and the clear orange liquor was cooled and extracted 4 times with chloroform (100 c.c.). The dried (Na₂SO₄) extract was freed from chloroform to give a brown oil (32 g.; 57%) which crystallised completely. It formed colourless needles, m. p. 74–76°, from ethyl alcohol after treatment with charcoal (Found: C, 64.65; H, 4.65; N, 9.45. $C_8H_7O_2N$ requires C, 64.5; H, 4.7; N, 9.4%).

β -2-Furoylpropionic Acid (IV).—The nitrile (2 g.) was refluxed for 1 hour with 18% hydrochloric acid (20 c.c.), charcoal was added, and after a further 10 mins. refluxing the liquor was diluted with water (50 c.c.), filtered, and the light yellow solution concentrated. The acid (2.1 g., 93%) separated as yellow grains. It had m. p. 115° and was pure. On recrystallising from hot water it was obtained as almost colourless, glistening flakes, m. p. 115°, lowered to 106° with previous softening on repeated crystallisation (Found: C, 57.25; H, 4.75. $C_8H_7O_4$ requires C, 57.15; H, 4.75%).

The acid (2 g.) was boiled for 15 minutes with 10% ethyl-alcoholic sulphuric acid (10 c.c.), cooled, and poured into water. The precipitated oil crystallised rapidly. The ethyl ester formed glistening, colourless plates, m. p. 52–53°, from aqueous alcohol (Found: C, 61.05; H, 5.95. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.1%).

3-Keto-6-(2'-furyl)-2:3:4:5-tetrahydropyridazine (V).— β -2-Furoylpropionic acid (1.68 g.; 0.01 mol.), aqueous hydrazine hydrate (1 c.c. of 85%), and ethyl alcohol (5 c.c.) were refluxed for 1 hour, then diluted with water (100 c.c.). The pyridazine which separated formed yellow, glassy needles, m. p. 145°, from ethyl alcohol (Found: C, 58.8; H, 4.7; N, 17.0. $C_8H_8O_2N_2$ requires C, 58.55; H, 4.9; N, 17.1%).

β -2-Thienoylpropionitrile (III; R = 2-C₄H₃S).—2-Thienyl β -dimethylaminoethyl ketone hydrochloride (2.2 g.; 0.01 mol.) (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, 64, 453), potassium cyanide (1.3 g.; 0.02 mol.), and boiling water (52 c.c.) were heated under reflux for 20 minutes. On cooling, the nitrile (0.7% yield) crystallised. It formed colourless needles, m. p. 66°, from benzene-light petroleum (Found: N, 8.4; S, 19.2. C_8H_7ONS requires N, 8.5; S, 19.45%). The acid, obtained on hydrolysis of the nitrile, formed flat needles, m. p. 120°, alone, and mixed with a specimen prepared from thiophen and succinic anhydride (Fieser and Kenelly, *J. Amer. Chem. Soc.*, 1935, 57, 1615) (Found: S, 17.3. Calc. for $C_8H_7O_2S$: S, 17.4%).

2-Benzofuryl β -Cyanooethyl Ketone (VI).—2-Benzofuryl β -dimethylaminoethyl ketone hydrochloride (5.07 g.), potassium cyanide (5.2 g.), and boiling water (130 c.c.) were refluxed for 10 minutes. The hot aqueous layer was decanted from an oil which thickened on chilling. The chilled aqueous layer deposited a mass of crystals which formed colourless needles, m. p. 110–111°, after repeated recrystallisation from methyl alcohol, in 21% yield. The oil was not investigated further (Found: N, 6.9. $C_{12}H_{13}O_2N$ requires N, 7.05%). The acid formed faintly yellow needles, m. p. 148°, from hot water (Found: C, 65.75; H, 4.55. $C_{12}H_{13}O_4$ requires C, 66.05; H, 4.6%).

Chloroimide from β -Benzoylpropionitrile (VIII).—The nitrile (10 g.) and dry benzene (50 c.c.) were cooled in ice, and a rapid stream of dry hydrogen chloride passed into the suspension. The solid dissolved, and crystals soon commenced to separate. After 30 minutes the solid was collected, washed with dry ether, and dried rapidly in a vacuum. The chloroimide salt (7.2 g.) formed pale yellow leaflets, m. p. 99° (efferv.) (Found, for the freshly prepared substance: C, 52.0; H, 4.95; N, 6.35; Cl, 29.6. $C_{10}H_{11}ONCl_2$ requires C, 51.75; H, 4.75; N, 6.05; Cl, 30.55%). On standing over aqueous potassium hydroxide for 14 days the original nitrile, m. p. 76°, was recovered.

Ethyl β -Benzoylpropimino-ether Hydrochloride (VII).—(a) The nitrile (25 g.) was suspended in ethyl alcohol (50 c.c.), and a rapid stream of dry hydrogen chloride was passed into the suspension cooled in ice. The temperature rose to 40°, the solid dissolved, and a deep yellow colour developed. When

saturated, the solution was left to stand for 1 hour, and the salt was precipitated by addition of dry ether. It formed colourless needles, m. p. 130°, in 60% yield after recrystallisation from cold ethyl alcohol-ether. The yield was not improved by keeping the reaction temperature below 10° (Found: C, 58.95; H, 6.7; N, 5.95; Cl, 14.55. $C_{12}H_{10}O_2NCl$ requires C, 59.5; H, 6.65; N, 5.8; Cl, 14.7%).

(b) The chloroimide hydrochloride (VIII) was dissolved in a minimum of hot ethyl alcohol, chilled immediately, and (VII) precipitated as colourless needles, m. p. 130°, by the addition of ether.

The base was obtained as an oil on adding aqueous sodium carbonate to an aqueous solution of the salt. It solidified rapidly and was obtained as colourless, glassy crystals, m. p. 60°, from light petroleum. The crystals turned magenta on keeping (Found: C, 70.4; H, 7.2; N, 7.05. $C_{12}H_{10}O_2N$ requires C, 70.5; H, 7.2; N, 6.85%).

Methyl β -Benzoylpropimino-ether Hydrochloride.—This salt was obtained from (VIII), in the same way as the ethyl homologue, by using methyl alcohol as solvent. It formed colourless needles, m. p. 127°, from methyl alcohol-ether (Found: Cl, 15.55. $C_{11}H_{10}O_2NCl$ requires Cl, 15.6%).

Ethyl β -4-Methoxybenzoylpropimino-ether Hydrochloride.— β -4-Methoxybenzoylpropionitrile (5 g.) and ethyl alcohol (10 c.c.) were treated with dry hydrogen chloride whilst cooling in ice. Precipitation of the salt commenced after a short time and was completed by addition of dry ether. It (5.5 g., 77%) was dissolved in absolute alcohol, the solution saturated with hydrogen chloride, and the salt reprecipitated by ether. It formed colourless needles, m. p. 133° (effervescence) (Found: Cl, 12.1. $C_{13}H_{14}O_3NCl$ requires Cl, 13.1%). On dissolving the salt in alcohol containing 1% water, β -4-methoxybenzoylpropionamide separated. It formed glistening plates or flat needles, m. p. 136°, from ethyl alcohol (Found: C, 63.95; H, 6.2; N, 6.55. $C_{11}H_{12}O_3N$ requires C, 63.75; H, 6.35; N, 6.75%).

β -4-Hydroxybenzoylpropionamide.—The imino-ether hydrochloride prepared analogously from β -4-hydroxybenzoylpropionitrile was dissolved in ethyl alcohol containing 1% of water, and on cooling the amide separated. It formed colourless irregular crystals, m. p. 218° (blue at 210°), from ethyl alcohol (bluish solution) (Found: N, 7.8. $C_{10}H_{11}O_3N$ requires N, 7.5%).

Decomposition of (VII).—(a) The hydrochloride (VII) (3.9 g.) was refluxed in absolute alcohol (20 c.c.) for 30 minutes. The solution turned orange, and ammonium chloride (0.4 g.) separated. On concentration a further crop (0.2 g.) separated. This represented 70% of the total nitrogen. The residue gave an oil on dilution with water, which solidified almost completely. It formed long, orange needles, m. p. 150° (0.6 g.), from ethyl alcohol (Found: C, 76.0; H, 6.1; N, 4.9%).

(b) The same hydrochloride (10 g.) was dissolved in concentrated hydrochloric acid (10 c.c.) and water (20 c.c.), and warmed on the steam-bath. The oil which slowly separated was taken up in ether, dried, and distilled. It (7.5 g.) had b. p. 165°, and was ethyl β -benzoylpropionate (Found: C, 69.6; H, 7.0. Calc. for $C_{13}H_{14}O_3$: C, 70.0; H, 6.8%).

N- β -Benzoylpropionylacetamide (IX).—Ethyl β -benzoylpropimino-ether (1 g.) and acetic anhydride (10 c.c.) were heated for 2 hours on the steam-bath. On decomposition with water, an oil was obtained which partly crystallised. It formed colourless, silky needles, m. p. 139–140°, from ethyl alcohol (Found: C, 65.9; H, 6.0; N, 6.3. $C_{12}H_{13}O_3N$ requires C, 65.75; H, 5.95; N, 6.4%).

Bis-3-(2-ethoxy-5-phenylpyrrole)methin Hydrochloride (X; n = 0).—Ethyl β -benzoylpropimino-ether hydrochloride (4.83 g.; 0.02 mol.), ethyl orthoformate (5.92 g.; 0.04 mol.), and 99% ethyl alcohol (10 c.c.) were refluxed for 15 minutes, by which time the whole had solidified to a mass of red needles. From ethyl alcohol this formed bright red needles, m. p. 175–176°, turning bronze on contact with air (Found: C, 71.2; H, 5.9; N, 6.95; Cl, 8.65. $C_{22}H_{25}O_2N_2Cl$ requires C, 71.5; H, 5.95; N, 6.65; Cl, 8.45%). Its absorption maximum in methyl alcohol lies at 4700 Å. After standing in contact with moist air for 48 hours it shows no absorption peak. Its sodium hydroxide-methyl alcohol solution also give a maximum absorption at 4700 Å. and an absorption curve almost identical with that of the freshly prepared dye in neutral or acid solution. The mother-liquor, freed from dye, deposited yellow needles, m. p. 150°, identical with the product obtained by heating the starting material in ethyl alcohol.

Bis-3-(2-methoxy-5-phenylpyrrole)methin Hydrochloride.—Prepared in the same way as the ethoxy-analogue, but with methyl alcohol as solvent, the dye formed red needles, m. p. 176° (for the freshly prepared substance; 163–164°, after standing in air for 1 hour), on recrystallisation from methyl alcohol (Found: Cl, 9.0. $C_{22}H_{21}O_3N_2Cl$ requires Cl, 9.05%).

Bis-3-(2-ethoxy-5-4'-methoxyphenylpyrrole)methin Hydrochloride.—Ethyl β -4-methoxybenzoylpropimino-ether hydrochloride (2.7 g.), ethyl orthoformate (3.0 g.), and ethyl alcohol (25 c.c.) were refluxed for 30 minutes. The red solution had, by this time, become brown, owing to complete crystallisation of the dye. It is very insoluble and was purified by boiling with *n*-butyl alcohol for 15 minutes and collecting whilst hot. It formed green crystals, m. p. 266° (Found: N, 6.05; Cl, 7.65. $C_{27}H_{29}O_4N_2Cl$ requires N, 5.8; Cl, 7.35%).

Bis-3-(2-ethoxy-5-phenylpyrrole)trimethin Hydrochloride (X; n = 1).—Ethyl β -benzoylpropimino-ether hydrochloride (2.4 g.; 2 mols.), β -ethoxyacetaldehyde acetal (0.8 g.; 1 mol.), and ethyl alcohol (10 c.c.) were refluxed for 10 minutes. The blue solution had then deposited crystals of the dye. They (0.4 g.) were collected after cooling and obtained as green crystals, m. p. 162°, from ethyl alcohol (Found: C, 72.65; H, 6.05; N, 6.0; Cl, 7.55. $C_{27}H_{29}O_4N_2Cl$ requires C, 72.55; H, 6.05; N, 6.25; Cl, 7.95%). In moist methyl alcohol the dye shows a maximum absorption at 4750–4800 Å.; in methyl alcohol containing a little concentrated hydrochloric acid the maximum lies at 6050 Å.; in methyl alcohol containing a little aqueous sodium hydroxide the maximum is also at 6050 Å. but fades rapidly.

225. β -Cycloylpropionitriles. Part II. Conversion into Bis-2-(5-cyclopyrrole)azamethin Salts.

By EDWARD B. KNOTT.

The blue dyes obtained by heating β -cycloylpropionitriles with hydroxylamine salts are salts of bis-2-(5-cyclopyrrole)azamethin (II; R = cyclyl, R' = H). One of the dyes (II; R = Ph, R' = H) was also prepared from α -cyano- β -benzoylpropionic acid and hydroxylamine hydrochloride. Bis-2-(3:5-diphenylpyrrole)azamethin (II; R = R' = Ph) (Rogers, *J.*, 1943, 590) was prepared similarly from β -benzoyl- α -phenylpropionitrile. The new dyes exhibit remarkable colour reactions with concentrated sulphuric acid.

THE remarkable stability of the 2-bis-(3:5-diarylpyrrole)azamethins (II; R = R' = aryl), discovered by Rogers (*loc. cit.*; B.P. 544,101) and less accurately named 2:2':4:4'-tetra-aryldipyrroazamethins by him, prompted the search for similarly constituted products, simpler in nature and of higher general solubility.



One of the methods employed by Rogers for the preparation of the above dyes consisted in heating β -aroyl- α -arylpropionitriles (I; R, R' = aryl) with ammonium formate in the presence of air, whilst Davies and Rogers (*J.*, 1944, 126) heated the same nitriles with formamide to obtain formylated 2-amino-3:5-diarylpyrroles, which can be used as intermediates for the above dyes. Although Rogers had not treated the simple β -aroylpropionitriles (I; R = aryl, R' = H) with either reagent in the expectation of obtaining dyes (II; R = aryl, R' = H), he had found that γ -nitrobutyrophenone gave no dye of this type under conditions which, when applied to γ -nitro- β -arylbutyrophenones, gave good yields of dye (II; R, R' = aryl).

Since a variety of β -cycloylpropionitriles were readily available by the method described in Part I (preceding paper), an investigation of their possible use as intermediates was undertaken.

On heating β -benzoylpropionitrile with ammonium formate in the presence of air at various temperatures, no trace of dye formation could be observed, nor could any formylated 2-amino-5-phenylpyrrole be isolated from a formamide melt. These negative results thus fell into line with the behaviour of γ -nitrobutyrophenone (Rogers, *loc. cit.*). It appeared, therefore, that dye formation required, not only a β -aroyl group in the starting nitrile (where R = Me, R' = aryl, no dye was formed; Rogers, *loc. cit.*, p. 595), but also an α -substituent (aryl?).

It is known, however (Biedermann, *Ber.*, 1891, 24, 4071; Tiemann, *ibid.*, p. 4077), that β -benzoylpropionamide (III; R = Ph) shows a tendency on fusion or dissolution to give a blue coloration, and this was also observed (see Part I) on melting or recrystallising β -*p*-hydroxybenzoylpropionamide. It was also noticed that, in attempting to form the amidine from ethyl β -benzoylpropimino-ether hydrochloride (IV; R = Ph) by solution in alcoholic ammonia and also on boiling (IV) with aqueous ammonia, a blue colour developed. There seemed, therefore, the possibility that this colour could be attributed to the formation of dyes of type (II; R' = H).



It is also known (Klobb, *Ann. Chim. Phys.*, 1897, 10, 184; Bougault, *ibid.*, 1908, 15, 504) that α -cyano- β -benzoylpropionic acid (I; R = Ph, R' = CO₂H) gives a blue dye on evaporation of solutions of its salts or on acidification of an alkaline solution of the acid which has been in contact with air. Klobb also reported that the dye could be sublimed with some decomposition, the vapours being red. This stability to heat is possessed to a greater degree by Rogers's dyes. It seemed therefore possible that this dye also might belong to type (II), in which R' is a carboxyl group.

Attempts to prepare and purify the dyes from (III) or (IV) in sufficient quantities for analysis were unsuccessful, but the dye from (I; R = Ph, R' = CO₂H) was obtained in a small amount. It was insoluble in strong alkalis, but dissolved in concentrated sulphuric acid to give a pale yellow-green solution which gave blue flocks on pouring into water. In aqueous pyridine it was decolorised by sodium dithionite. It was almost insoluble in most

solvents but dissolved in nitrobenzene or pyridine giving a magenta solution. Analysis suggested the formula $C_{20}H_{14}O_2N_2$, which rules out the possibility of its belonging to the dipyrroazamethin class of dye. It is also readily prepared in low yield from β -benzoylpropionamide by a different method, and the proposed structure and mechanism of formation are discussed later. The non-identity of these dyes with dipyrroazamethins was disappointing, and work on the preparation of (II; $R' = H$) was about to be abandoned when, by chance, an unusual reaction was observed. Whilst engaged on the preparation of various derivatives of the β -aroylpropionitriles (I; $R' = H$) for their characterisation, difficulty was encountered in the formation of their oximes. Thus, β -benzoylpropionitrile (I; $R = Ph$, $R' = H$) failed to give an oxime with either hydroxylamine acetate or the base itself on refluxing in ethyl alcohol, most of the original nitrile being recovered unchanged. On refluxing an alcoholic solution of the nitrile with hydroxylamine hydrochloride, however, the mixture darkened and a brilliant blue coloration developed. When a large excess of the hydroxylamine salt was employed the dye crystallised during the refluxing, giving an almost solid mass of needles. The dye was slightly soluble in boiling water, the solution giving an immediate precipitation of silver chloride on addition of silver nitrate. It was soluble in alcohols, acetone, and pyridine. Analysis suggested the formula $C_{20}H_{15}N_3 \cdot 2HCl$. Its alcoholic solution when poured into water gave magenta flocks soluble in alcohol to a blue solution and which on purification gave a second blue dye of the formula $C_{20}H_{15}N_3 \cdot HCl$. Attempts to isolate the base were fruitless since, although it had some stability in solution, it readily decomposed on attempted isolation. The dye salts were very stable to boiling concentrated hydrochloric acid, dissolved in concentrated sulphuric acid to give a blue solution, and were reduced to a colourless leuco-compound by sodium dithionite. The leuco-compound was reoxidised by aerial oxygen to a blue dye. The salts did not sublime on heating under reduced pressure. Apart from the last property (which might be expected of the salts) the behaviour of these dyes is similar to that of Rogers's dye (II; $R = R' = Ph$), and the analysis agrees well with their being the *dihydrochloride* and *monohydrochloride* of bis-2-(5-phenylpyrrole)azamethin (II; $R = Ph$, $R' = H$). Degradation experiments with hydriodic acid, and with an acetic anhydride-sodium acetate mixture which discharged the colour, did not lead to any definite products. Rogers (*loc. cit.*) proved the constitution of his dyes by an alternative synthesis which consisted in the condensation of 3:5-diphenylpyrrole with 2-nitroso-3:5-diphenylpyrrole. Nitrosation of 2-phenylpyrrole, however, either with nitrous acid or with alkaline amyl nitrite, failed to give a pure nitroso-derivative. The dark green solid obtained when employing nitrous acid gave a magenta dye on heating with 2-phenylpyrrole in acetic anhydride-acetic acid mixtures but not in sufficient quantities for isolation. Since 2-phenylpyrrole is readily converted into a magenta dye in the presence of mineral acids and acetic anhydride, it is possible that the green solid causes dye formation by virtue of its being a hydrochloride. Alternatively, if nitrosation occurs in the β -position, as is usual with pyrroles (cf. Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, p. 104), the interaction of 4-nitroso-2-phenylpyrrole hydrochloride with 2-phenylpyrrole might well lead to a magenta dye. The structure of the dye was proved beyond reasonable doubt, however, by obtaining analogously bis-2-(3:5-diphenylpyrrole)azamethin (II; $R, R' = Ph$) from β -benzoyl- α -phenylpropionitrile and hydroxylamine hydrochloride. The reaction proceeded best in boiling butanol to give the unstable dye salt, or in ethylene glycol at 120° to give the dye base. It was also found to proceed rapidly to give a low yield of dye on using formamide as solvent. The salt rapidly lost hydrogen chloride on contact with the atmosphere. The base had all the properties of the dye prepared according to Rogers (*loc. cit.*) and analysis confirmed the identity.

The instability of the new dye base may explain the non-formation of dye on heating γ -nitrobutyrophenone and ammonium formate (Rogers, *loc. cit.*), although further attempts at dye formation by this reaction in the presence of salts such as ammonium chloride or hydroxylamine hydrochloride also failed.

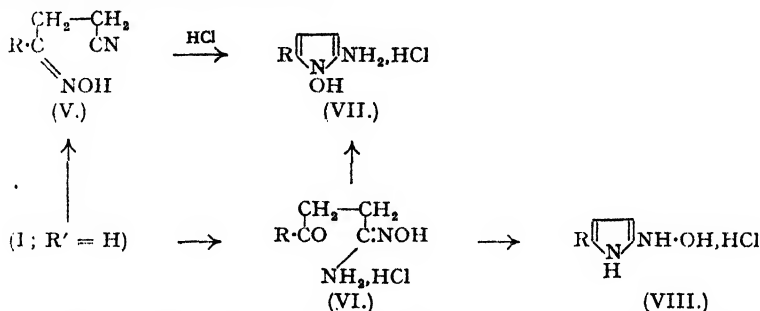
β -Benzoylpropionitrile and hydroxylamine sulphate gave bis-2-(5-phenylpyrrole)azamethin sulphate.

The reaction was then applied to a variety of β -cycloylpropionitriles in order to determine its scope. In every case β -aroylpropionitriles gave the required dye. β -2-Thienoylpropionitrile (I; $R = 2-C_4H_3S$, $R' = H$) gave the corresponding dye in low yield, but β -2-furoylpropionitrile and 2-benzofuryl 2-cyanoethyl ketone gave only brown solutions on similar treatment.

On heating α -cyano- β -benzoylpropionic acid (I; $R = Ph$, $R' = CO_2H$) with alcoholic hydroxylamine hydrochloride a blue, alkali-insoluble dye resulted. Its analysis, and physical

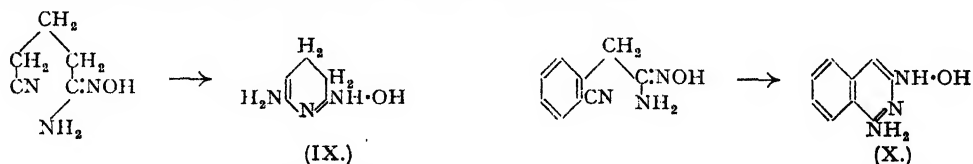
and chemical properties, showed that it was identical with the dye obtained from β -benzoylpropionitrile. The loss of carbon dioxide took place before dye formation occurred, a copious evolution being observed on heating the reactants at 95° in butenol. It is possible that the substituted pyrrole- β -carboxylic acid which may be an intermediate in the dye formation, like other such acids, is readily decarboxylated (cf. Ciamician, *Ber.*, 1880, **13**, 2235; 1881, **14**, 1054).

The mechanism of the reaction is obscure, since no intermediates could be isolated. The first stage reaction could take place in two ways, either by oxime formation (V), or by hydroxylamine addition to the nitrile group to give an amidoxime (VI). At this stage, cyclisation in two ways might occur to give either 2-amino-1-hydroxy-5-R-pyrrole (VII) or 2-hydroxylamino-5-R-pyrrole (VIII) hydrochlorides.

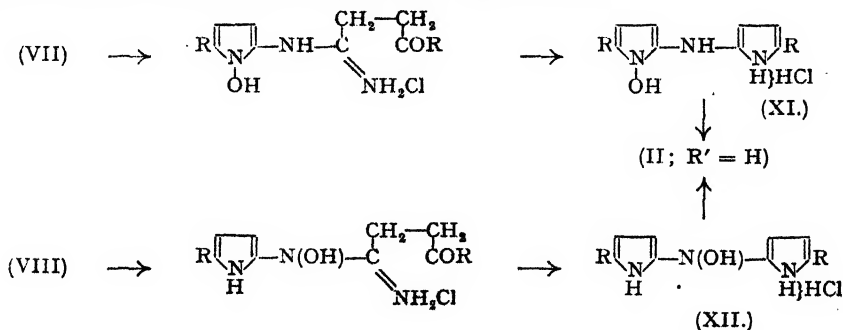


Oxime formation would appear to be the natural step, but it is significant that under no conditions could an oxime be isolated. It is well known (Nordmann, *Ber.*, 1884, **17**, 2747; Tiemann, *Ber.*, 1884, **17**, 126, 1685; 1886, **19**, 1475; 1889, **22**, 2391, 2942, etc.) that aliphatic nitriles, particularly those which are also readily hydrolysable, react with hydroxylamine or its salts to yield amidoximes. Thus the formation of (VI) is quite feasible, although under conditions used by Tiemann no product could be isolated.

There are no indications of the second-stage reaction, although it is known that γ -diketones will react with hydroxylamine to give substances analogous to (VII) (Knorr, *Annalen*, 1886, **286**, 296). It is also known that hydroxylamine will react with 1:3-dicyanopropane (Tiemann, *Ber.*, 1889, **22**, 2945; Biedermann, *ibid.*, p. 2967) or *o*-cyanobenzyl cyanide (Eichelbaum, *ibid.*, p. 2973) to give substances which are not the expected amidoximes, as they are insoluble in alkali. It is possible that cyclisation occurred, not as proposed by the above authors, but so as to give a dihydropyridine (IX) and an isoquinoline (X).



Such ring closures would then be analogous to the formation of (VIII). The third-stage reaction could proceed from either (VII) or (VIII) by addition of a further nitrile molecule followed by cyclisation and elimination of water to give the dye.



The precipitation of the dihydrochloride, which is more soluble in alcohol than the monohydrochloride, is difficult to explain, since it is unlikely that the dye is a stronger base than hydroxylamine.

Rogers (*loc. cit.*) found that 2-amino-3:5-diphenylpyrrole is readily oxidised to the azamethin, but such a mechanism for dye formation cannot be applied here, since no oxygen is present. He found also that 2-nitroso-3:5-diphenylpyrrole gives the azamethin on heating, and it is possible that (VIII) may also undergo self-condensation with the elimination of water and hydroxylamine.

All the dye salts gave similar blue solutions in organic solvents but differed in colour in the crystalline state. Striking differences, however, were shown in their behaviour towards concentrated sulphuric acid. The different colours given in hot and cold sulphuric acid and on precipitating the dye from the latter with water allow the identification of nearly all the dyes so far prepared (see Table I).

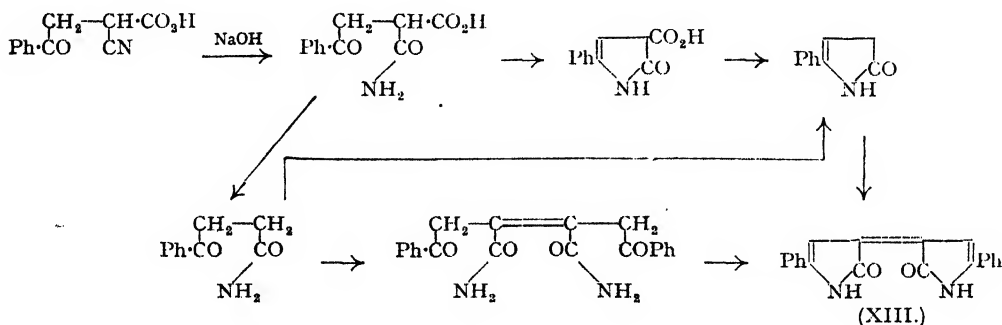
TABLE I.

II.	Cold H ₂ SO ₄ .	Addition to water.	Hot H ₂ SO ₄ .
R' = H, R =			
Phenyl	Blue *	Magenta	Green → yellow
<i>p</i> -Tolyl	Green	Blue	Yellow → brown
<i>p</i> -Chlorophenyl	Blue	Blue	Green → yellow → brown
<i>p</i> -Bromophenyl	Blue	Blue	Yellow → red-yellow
<i>p</i> -Hydroxyphenyl	Orange	Magenta	Red
<i>p</i> -Methoxyphenyl	Orange	Blue-green	Red
<i>m</i> -Hydroxyphenyl	Purple	Magenta	Blue → yellow
<i>m</i> -Methoxyphenyl	Purple → blue	Magenta	Blue → yellow
3 : 4-Dimethoxyphenyl	Orange	Blue	Brown → red → brown
1-Naphthyl	Yellow → purple → blue	Blue	Blue → green → yellow
2-Naphthyl	Yellow " " "	Blue	Blue " " "
2-Thienyl	Green	Blue	Red → yellow
R = R' = Phenyl	Blue	Blue	Green → yellow

* Sulphate gave green solution.

As stated above, the dye obtained by Klobb from α -cyano- β -benzoylpropionic acid does not belong to the azamethin class. Apart from the analysis figures, the pale colour it gives in concentrated sulphuric acid is quite different from the deep colours given by (II). An alternative synthesis was found whilst experimenting with β -benzoylpropionamide with a view to the preparation of the dye observed on fusing the latter. Whereas alcoholic hydroxylamine salts did not give any dye on refluxing them with the amide, yet on replacing the alcohol by formamide and heating to 120° the latter reacted suddenly with the hydroxylamine hydrochloride (shown by separate experiment) with the evolution of ammonia, probably due to the formation of a hydroxamic acid (cf. Hoffmann, *Ber.* 1889, **22**, 2854), and a secondary reaction caused the separation of a crystalline dye. The same dye was formed in very small amounts when the hydroxylamine hydrochloride was omitted. The dye had all the properties of Klobb's dye and analysis confirmed the identity.

Insufficient data have been collected on the dye to prove its structure, but it is suggested that it belongs to the *isoindigotin* class (cf. Wahl and Bagnard, *Bull. Soc. chim.*, 1909, 5, 1039).



1914, 15, 329). Analysis agrees with its being *bis*-3-(2-*keto*-5-*phenyl*-2 : 3-*dihydropyrrolylidene*) (XIII). Its formation from (I; R = Ph, R' = CO₂H) can be explained by hydrolysis by

alkali to the amide, followed by cyclisation, decarboxylation, and oxidation, or by decarboxylation, oxidation, and cyclisation as shown. The hydroxylamine salt-formamide process involves oxidation at one stage and it is not clear how this takes place.

The same dye is also readily formed from β -benzoylpropionamide, acetamide, and hydroxylamine hydrochloride, and the β -benzoylpropionamide may be replaced by the acid or ester. Lævulic acid did not give any dye under similar conditions.

EXPERIMENTAL.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.s are uncorrected.)

Bis-2-(5-phenylpyrrole)azamethin Dihydrochloride.—(a) β -Benzoylpropionitrile (15.9 g., 0.1 mol.), hydroxylamine hydrochloride (28 g., 0.4 mol.), and industrial methylated spirit (150 c.c.) were refluxed for 2 hours. After the semi-solid reaction mixture had cooled, the dye was collected and washed well with acetone. The yield of crude solid (16.2 g.) was 87.7%. The filtrate gave hydroxylamine hydrochloride (10.1 g.) on concentration. If boiling butanol is used as the solvent a magenta dye is also formed. It is readily removed, however, by washing with acetone. The dye, recrystallised from pyridine, formed purple needles of no definite m. p. (Found: C, 64.4; H, 5.05; N, 11.2; Cl, 20.2. $C_{20}H_{17}N_3Cl_2$ requires C, 64.85; H, 4.6; N, 11.35; Cl, 19.15%). The monohydrochloride was obtained as short needles from butanol or pyridine by pouring an alcoholic solution of the dihydrochloride into water (Found: C, 71.73; H, 4.8; N, 12.5; Cl, 10.5. $C_{20}H_{16}N_3Cl$ requires C, 71.95; H, 4.8; N, 12.6; Cl, 10.65%). The sulphate, obtained in low yield (37%) from the nitrile and hydroxylamine sulphate, was very insoluble in most organic solvents. It was obtained as small bronze needles (Found: N, 10.5. $C_{20}H_{17}O_4N_3S$ requires N, 10.65%).

(b) α -Cyano- β -benzoylpropionic acid hydrate (2.2 g., 0.01 mol.), hydroxylamine hydrochloride (1.4 g., 0.02 mol.), and industrial methylated spirit (10 c.c.) were refluxed for 90 minutes. The dye (1.0 g., 54%) was collected after cooling and recrystallised from pyridine. It formed alkali-insoluble purple needles (Found: C, 64.25; H, 5.0; N, 11.5%).

Bis-2-(3:5-diphenylpyrrole)azamethin.—(a) β -Benzoyl- α -phenylpropionitrile (4.7 g., 0.02 mol.), hydroxylamine hydrochloride (1.4 g., 0.02 mol.), and ethylene glycol (20 c.c.) were heated at 120° in an oil-bath for 2 hours. The dye separated as coppery crystals. These were collected when cold, and recrystallised from nitrobenzene forming short needles (0.3 g., 6.7%), m. p. 286° (Found: C, 84.9; H, 5.05; N, 9.5. Calc. for $C_{22}H_{18}N_3$: C, 85.5; H, 5.1; N, 9.4%). (b) With the same procedure as in (a) but using *n*-butyl alcohol (20 c.c.) as solvent and refluxing for 2 hours, the deep blue solution deposited the dye salt on chilling. The purple solid rapidly acquired a coppery sheen on standing in the atmosphere, owing to hydrolysis to the base (m. p. 286°) (1.2 g.; 26.7%). (c) The nitrile (4.7 g.), hydroxylamine hydrochloride (1.4 g.), and formamide (20 c.c.) were placed in an oil-bath at 120°. The temperature of the mixture rose to 90°, then with evolution of gas the temperature rose to 150° and the dye separated. It (0.8 g., 17.8%) was collected after dilution with alcohol, ground with alcohol, and washed with alcohol and water. It had m. p. 286° and was identical with the sample prepared according to (a).

TABLE II.

II; R' = H, R =	Yield, %	Solvent.	Crystal form.	Formula.	Found.	Requires.
<i>p</i> -Tolyl	49.8	Acetic acid	Short bronze needles	$C_{22}H_{21}N_3Cl_2$	N, 10.4	10.55
<i>p</i> -Bromophenyl.....	41.5	Acetic acid	Short gold-green needles	$C_{20}H_{15}N_3Cl_2Br_2$	N, 7.5	7.95
<i>p</i> -Chlorophenyl	55	Acetic acid	Fine purple needles	$C_{20}H_{15}N_3Cl_4$	N, 9.5	9.6
<i>p</i> -Hydroxyphenyl *	—	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	C, 60.05 H, 4.2 N, 10.9 Cl, 17.1	59.7 4.25 10.45 17.65
<i>p</i> -Methoxyphenyl ...	57	Pyridine	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	C, 60.65 H, 5.3 N, 9.55 Cl, 16.15	61.4 4.9 9.75 16.5
<i>m</i> -Hydroxyphenyl †...	40	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	N, 10.55	10.45
<i>m</i> -Methoxyphenyl ...	46.5	Acetic acid	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	N, 9.45	9.75
3:4-Dimethoxyphenyl	52	Pyridine	Coppery needles	$C_{24}H_{23}O_4N_3Cl_2$	N, 8.5	8.55
1-Naphthyl	44.5	Pyridine	Purple threads	$C_{28}H_{21}N_3Cl_2$	C, 71.55 H, 4.65 N, 9.15	71.5 4.45 8.95
2-Naphthyl	37	Pyridine	Purple needles	$C_{28}H_{21}N_3Cl_2$	N, 9.2	8.95
2-Thienyl	23	Acetic acid	Short green needles	$C_{18}H_{13}N_3S_2Cl_2$	N, 10.45 S, 16.35	11.0 16.8

* Soluble in alkali to green solution.

† Soluble in alkali to blue solution.

Hydroxylamine Hydrochloride and β -Benzoylpropionamide.—The amide (7.08 g., 0.04 mol.), hydroxylamine hydrochloride (2.8 g., 0.04 mol.), and formamide (20 c.c.) were placed in an oil-bath at 120°. After a while the evolution of gas commenced and the dye separated rapidly. After 5 minutes the melt was diluted with alcohol, and the dye collected, and washed with alcohol until the washings were

colourless. It (0.5 g.) formed brassy, irregular plates from pyridine, in which it gives a magenta solution. It sublimed with some decomposition, giving red vapours. It was readily decolorised in pyridine solution with aqueous sodium dithionite (Found: C, 75.7; H, 4.6; N, 9.0. $C_{20}H_{14}O_2N_2$ requires C, 76.45; H, 4.45; N, 8.9%).

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[Received, November 28th, 1946.]

226. *The Photochemical Polymerisation of Vinyl Acetate Vapour.*

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The kinetics of the polymerisation of vinyl acetate vapour under the influence of ultra-violet light of wave-lengths greater than 2500 Å. have been investigated. Shorter wave-lengths cause decomposition of the molecule into products which inhibit the polymerisation. At high enough pressures the rate of polymerisation is proportional to the first power of the concentration of vinyl acetate and to the square root of intensity of the incident light. At pressures of about 20 mm. the rate falls off very rapidly and becomes immeasurably slow at lower pressures, e.g., 15 mm. This phenomenon is apparently due to the fact that the photo-excited vinyl acetate molecule can lose its energy before another molecule of monomer can add on. This hypothesis is reinforced by the effect of other added gases. Quite small amounts of oxygen and of butadiene retard the reaction by terminating the growing chain. Amounts of inert gases like helium, argon, and hydrogen comparable with the amount of vinyl acetate also retard the polymerisation but these gases function, not by stopping growing chains, but by deactivating by collision the photo-excited vinyl acetate molecule.

THIS paper is a continuation of the work on the systematic examination of polymerisation reactions in the vapour phase. In practically every example of a vinyl derivative that readily polymerises in the vapour phase a number of unique observations have been made which have helped in elucidating the kinetics of such reactions. As will be seen below, the vinyl acetate reaction is no exception. As with methyl methacrylate and chloroprene, it happens that there are two distinct mechanisms whereby macromolecules are formed, and it turns out that it is easy to separate the two modes of polymerisation. Apart from these considerations, however, the polymerisation of vinyl acetate has been studied in the liquid phase, peroxide catalysts (Cuthbertson, Gee, and Rideal, *Proc. Roy. Soc.*, 1939, *A*, **170**, 300; Blaikie and Crozier, *Ind. Eng. Chem.*, 1936, **28**, 1155; Skirrow, *British Plastics*, 1939, **10**, 416, 507; Starkweather and Taylor, *J. Amer. Chem. Soc.*, 1930, **52**, 4708) and ultra-violet radiation (Taylor and Vernon, *ibid.*, 1931, **53**, 2527) being used. The results of these investigations are not sufficiently comprehensive to enable a decision to be made as to whether the mechanisms in the liquid phase are the same for photo- and peroxide-catalysed reactions: nor is it possible to say whether the mechanism in the gas phase is kinetically similar to that in the liquid phase.

It has been shown that in some dimerisations, e.g., of cyclopentadiene (Wassermann, *J.*, 1939, 362, 367, 371, 375), the bimolecular constants are the same in the liquid and in the vapour phase, and hence it seemed necessary to see whether in a suitable polymerisation process a similar identity of rates could be obtained. Vinyl acetate is one of the few monomers which polymerise equally well in both phases, and thus some information on this point might be obtained.

There is, however, another important reason for undertaking this work. In the liquid phase it is believed that polymerisation occurs by the free-radical mechanism, i.e., the active polymer is a large free radical. Although it has been demonstrated that a free radical mechanism *can* occur in the liquid phase, it is by no means certain that every liquid-phase polymerisation proceeds by this mechanism. As will be shown, it is possible to characterise the free-radical polymerisation of vinyl acetate in the vapour phase. If therefore it can be shown that there is in fact a correlation in behaviour of vinyl acetate between the two phases, it may be possible to gain some more precise information about the behaviour in the liquid phase. The present paper is confined to the gas-phase polymerisation, and further communications will deal with the liquid-phase reaction. Polymerisation must be initiated by radiation, by excited mercury atoms, or by free radicals, since purely thermal polymerisation does not occur at all.

EXPERIMENTAL

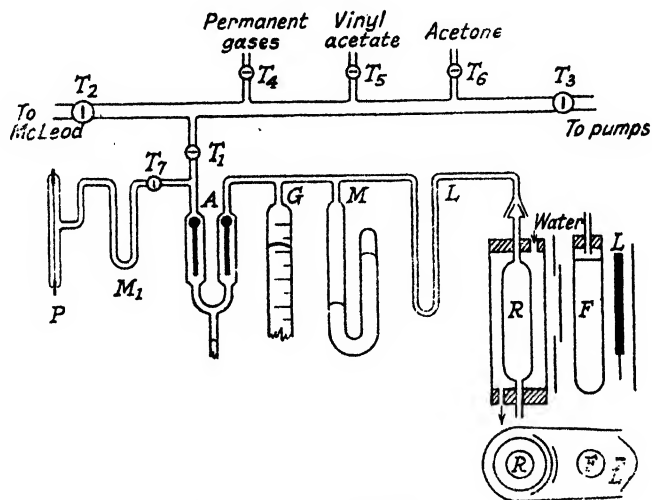
Apparatus.—The apparatus used calls for no special comment, the general arrangement being shown in Fig. 1. The silica reaction vessel was placed in a thermostat, and the polymerisation could be carried out at various temperatures up to 100° either under constant pressure of vapour, using a gas burette, or at constant volume, using a mercury manometer. Mercury cut-offs were employed to isolate the

reaction system to avoid trouble with greased joints. The apparatus was evacuated by a mercury diffusion pump. The sources of light were high- and low-pressure mercury lamps depending on the type of reaction being studied. Care was taken to ensure constancy of light output by controlling the voltage applied to the lamps. Experiment showed that, like other monomers, vinyl acetate is decomposed by the shortest wave-lengths emitted by the mercury lamp. Consequently it was necessary to screen off such radiation by acetic acid filters (30% aqueous solution). McLeod and Pirani gauges were used to measure the pressures of gases not condensable in liquid air.

Particular care was taken in the purification of vinyl acetate. This was originally obtained from Shawinigan Chemicals Ltd. and usually contained some acetaldehyde. The latter substance is a strong inhibitor of the liquid- and also the gas-phase polymerisation and hence its removal is essential. The monomer was first fractionally distilled twice at atmospheric pressure, only the 72–73° fraction being collected. The aldehyde is difficult to separate, and all fractions boiling below 72° were discarded. The nearly pure ester—which only gave a faint pink coloration with Schiff's reagent on standing for 5 minutes—was sealed into a tube on to the vacuum line of the apparatus. The ester was then frozen with liquid air and pumped out to 10^{-5} mm. It was melted and refrozen several times with evacuation between each cycle. Distillation was conducted in a vacuum, only the middle portion being used for experimental purposes.

"A.R." Acetone was used as a source of methyl radicals. It was freed from oxygen in a similar manner to the vinyl acetate. Oxygen came from potassium permanganate; hydrogen was purified by passing through palladium. Butadiene was taken from a cylinder and purified by vacuum distillation.

FIG. 1.



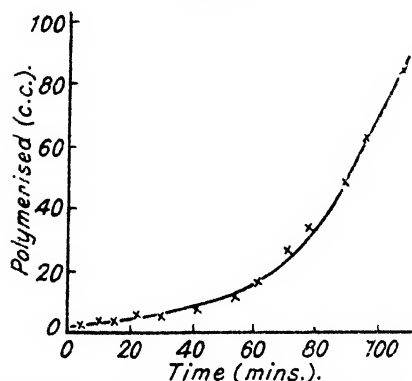
General arrangement of apparatus.

Direct Photo-reaction.—Several precautions have to be taken in measuring the velocity of polymerisation. Fig. 2 shows how the number of molecules polymerised increases with time of illumination, starting with a clean tube. There is a marked induction period, and gradually the rate attains a constant value. If illumination is prolonged, the rate begins to decrease again, but since this only occurs when very thick deposits of polymer are formed it is attributed to scattering and absorption of the effective radiation by the polymer. The long induction period is not due to the presence of gas-phase inhibitors, because a similar phenomenon is observed if successive separate portions of vinyl acetate are used. This points to an effect due to the reaction vessel itself. It is not due to the fact that the polymerisation really takes place in the deposited polymer. There are many reasons for supporting this contention. The customary mist of solid polymer is formed in the gas phase when the lamp is switched on, the polymerisation rate does not increase proportionally to the weight of polymer deposited, inert gases like helium, argon, and hydrogen inhibit the polymerisation, and the intensity exponent in the polymerisation does not tend to zero, as happens in the polymerisation of chloroprene where polymerisation does occur in the solid polymer. As will be shown later, there is little doubt that the induction period is due to the fact that the active polymer molecules are somehow destroyed when they collide with the clean silica walls, and that when these are covered by polymer there is more or less elastic reflection with a consequent lengthening of the chain until mutual destruction occurs in the gas phase. This suggestion is supported by covering the walls with a layer of Gelva 15—commercial polyvinyl acetate—whereby the induction period is diminished but curiously enough not completely eliminated. The other surprising fact is that walls need to be covered by a fairly thick layer of polymer. It might be expected that a monolayer of polymer would be sufficient. Assuming a degree of polymerisation of 100, a monolayer would correspond to a pressure decrease of 10^{-2} mm. whereas a very much greater decrease of pressure is required before the reaction rate is constant. Owing to the necessity for depositing polymer there is a measurable absorption of the monomer by the polymer, and as this amount of polymer increases so the amount of sorbed monomer increases. Corrections are

made for the total observed consumption of monomer to give the true photo-rate. In order to cut down corrections of this kind to a minimum, the method of bracketing must be employed, and tubes are used for a relatively small number of runs just after conditions have become relatively steady. Experiments show there is no measurable induction period and that there is no long-continued reaction in the dark, as occurs with methyl methacrylate. This is in accord with the present experience with molecules of the type $\text{CH}_2=\text{CHX}$. If a heavily coated tube is being used there is sometimes an apparent induction period or even a pressure increase, due apparently to some desorption of monomer from the polymer when the light is switched on.

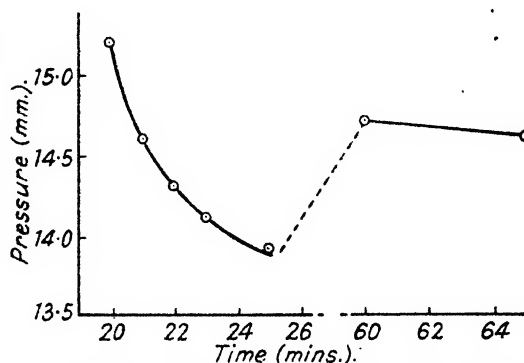
General Kinetics.—Decomposition. As has already been mentioned, unfiltered light from the mercury lamp leads to decomposition of the vinyl acetate, one of the products of decomposition being non-condensable in liquid air. This gas could only be hydrogen, carbon monoxide, or methane. A Pirani gauge was consequently calibrated by using carbon monoxide and hydrogen. The gas from vinyl acetate gave a calibration curve coinciding exactly with that for carbon monoxide. The calibration curve for methane lies very close to that for carbon monoxide and therefore it is difficult to say whether

FIG. 2.



Course of polymerisation at constant pressure starting with a clean tube.

FIG. 3.



Inhibition of polymerisation by the accumulated products of decomposition of vinyl acetate.

the gas is one or the other. The important point of this decomposition is that the products are strong inhibitors for the photo-polymerisation. This behaviour is shown most clearly by the following kind of experiment. Vinyl acetate is illuminated at constant volume for a given period and the rate measured. After this, the pressure is increased to the initial value and the run continued. As Fig. 3 shows, there is a very marked diminution in rate as a result of the accumulation of the products of decomposition. The acetic acid filter completely eliminates this decomposition, and hence it would appear that it has nothing to do with the polymerisation reaction. Another indication in support of this suggestion is that decomposition occurs just as readily below the critical pressure at which vinyl acetate ceases to polymerise. These observations are completely in accord with experience with methyl methacrylate and methyl acrylate. Short-wave radiation, instead of leading to activation and eventual starting of polymerisation, simply results in disruption of the molecule into products incapable of starting polymerisation.

Effect of pressure. The constant-pressure technique being used, the variation of rate with pressure was investigated, due regard being paid to corrections owing to disappearance of monomer by absorption by the polymer. A typical run is shown in Table I, the bracketing pressure being 42.1 mm. Similar

TABLE I.

Direct photo-polymerisation; temp. 20°; high-pressure Hg lamp.

Pressure (mm.).	Observed rate (in c.c./min.) at 42.1 mm. pressure.	Dark "rate" (c.c./min.).	Net polymerisation rate (c.c./min.).
42.1	25.6	0.8	24.8
42.1	27.3	1.9	25.4
37.5	22.1	—	22.1
23.9	3.56	—	3.56
42.1	26.5	1.4	25.1
48.4	31.6	2.0	29.6
55.6	40.4	1.6	38.8
42.1	30.4	2.0	28.4

series of runs were made over other ranges of pressure, the maximum being fixed at about 60 mm., the saturation vapour pressure of vinyl acetate. Rates relative to that at 42.1 mm. are plotted as a function of pressure in Fig. 4. The most striking feature of this plot is the appearance of a limiting pressure below which the reaction rate is immeasurably slow. At high enough pressures the rate is approximately proportional to the first power of the pressure, whereas in the intermediate region 20–40 mm.

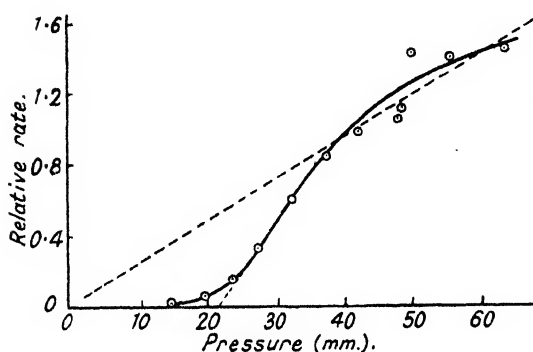
the rate = const. $(p - p_0)$, where p_0 may be defined as a critical pressure of about 21 mm. This limit has nothing to do with inhibition by decomposition products, for if the vapour is illuminated at, say, 20 mm. for a considerable period and the pressure is then raised to say 30 mm., polymerisation proceeds normally. Similarly, if polymerisation is occurring at 30 mm. and the pressure is reduced to 20 mm. polymerisation immediately ceases. To show this more clearly prolonged illumination with use of the acetic acid filter gave the following results:

Vinyl acetate pressure (mm.).	Time of illumination (mins.).	C.c. of vapour polymerised.	Pressure of products of decomposition (mm.) (non-condensable in liquid air).
12.9	120	—	4.0×10^{-2}
15.0	100	8.0	3.5×10^{-2}

It will be seen that a reduction in pressure of only 2 mm. reduces the very small rate of polymerisation at 0.08 c.c./min. to an immeasurable value, yet the decomposition is hardly affected. Likewise there is no photo-decomposition of the polymer and hence this could not be the cause of the appearance of the limit.

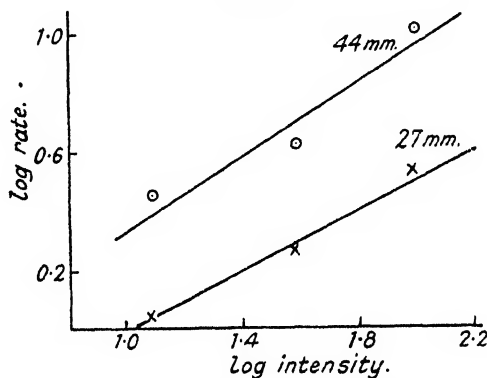
That the phenomenon has something to do with the initiation process is shown by the fact that if a low-pressure mercury lamp is used, and presumably therefore excited mercury atoms are responsible for starting polymerisation, the limit is displaced to a lower pressure at 12 mm.

FIG. 4.



Rate of polymerisation as a function of pressure.

FIG. 5.



Variation of rate with intensity of incident illumination.

Intensity exponent. The variation of polymerisation rate with intensity of light gives useful information in regard to the order of the process in which the active polymer molecule is destroyed. It is particularly important to measure this exponent in view of the gradual increase of rate with the amount of polymer deposited and the existence of the critical limit. The intensity was decreased by using perforated screens which had been previously calibrated by a photoelectric cell. Runs were made at high pressure where the rate is proportional to pressure and at as low pressure as possible to see whether in the vicinity of the limit there was any change in the mechanism of the termination process. A logarithmic plot of the results is given in Fig. 5. The slope of these curves is 0.60 and 0.55 for 44 and 27 mm., respectively, which is a sure indication that polymerisation stops when two active polymers mutually destroy each other. This again furnishes additional proof that the appearance of the limit has nothing to do with the termination process.

The same set-up being used, the value of the critical limit was measured for an intensity only one-eighth of that used in the measurements given on p. 1203. The following results give a limit on extrapolation of 21 mm. Thus, in spite of a diminution in rate of starting of polymerisation by a factor of 8 and an increase in chain length by a factor of 3, the limit is unaffected.

Vinyl acetate press. (mm.)	19.1	25.3	38.2	46.0
Rate (c.c./min.)	0.25	1.05	4.76	5.85

Effect of temperature. Rather a complicated procedure had to be adopted in these experiments, for at each temperature a series of runs at different pressure had to be made in virtue of the existence of the critical limit, since it was essential to find whether the limit itself was dependent on temperature. To ensure that the condition of the tube was as nearly similar as possible during these experiments, before and after each series of runs at elevated temperature standard runs were made at 20° and at 42 mm. pressure. It was not possible to go to temperatures greater than 100° since decomposition of the polymer led to complications and the rate fell off very quickly above this temperature. The results are summarised in Fig. 6, where the relative rates are plotted against pressure for a series of temperatures. At pressures above 30 mm. it will be seen that the rate decreases with increasing temperature. This phenomenon, although observed with methyl acrylate and methyl vinyl ketone, might be due to the intervention of some inhibitor or to a change in the nature of the termination reaction. Using a pressure of 60 mm. at 66°, a measurement of the variation of rate with intensity gave the following results:

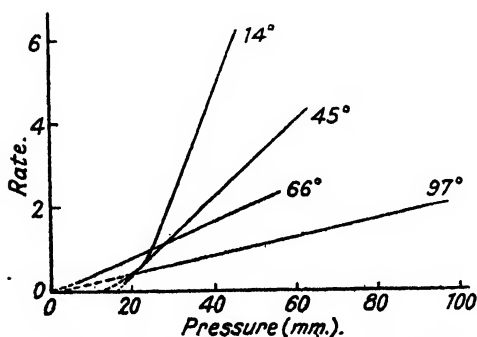
Intensity	1.00	0.384	0.125
Rate (mm./min.)	0.63	0.38	0.185

This corresponds to an exponent of 0.60, in agreement with the results at 20°. Hence, mutual termination of chains still operates at elevated temperatures. At each temperature the variation of rate with pressure is represented by the equation $\text{Rate} = k(p - p_0)$, except in the neighbourhood of the limit, defined for the sake of convenience by p_0 in this equation. The following results show how the value of p_0 varies with temperature:

Temp.	14.0°	46°	66°	97.0°
p_0 (mm.)	21.0	16.0	6.0	5.0

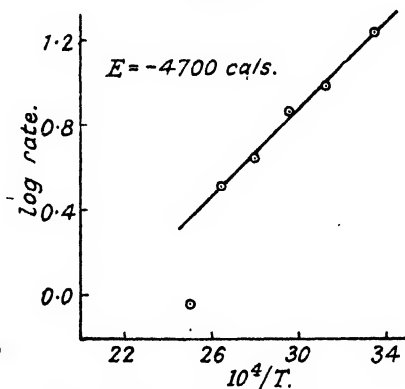
Hence, at above 100° the polymerisation pursues a normal course in which $R = \text{const. } (I_{\text{abs}})^{\frac{1}{2}} (M)$, which are kinetics compatible with the idea that all the light is absorbed and that mutual termination of the polymer chain occurs almost exclusively (Gee and Melville, *Trans. Faraday Soc.*, 1944, **40**, 240). Below 30° an inversion of the temperature coefficient occurs and the rate increases with increase in temperature. This kind of anomalous behaviour is, however, primarily due to the intervention of some reaction responsible for the appearance of the limit—a reaction which itself possesses a temperature coefficient. In absence of this complicating phenomenon, namely, at as high pressure as can be obtained, there is no doubt that the polymerisation rate decreases with increasing temperature. The temperature coefficient was therefore measured for a pressure of 50 mm. and the $\log \text{Rate}-1/T$ plot is shown in Fig. 7. The slope corresponds to an apparent energy of activation of -4700 cal. The point at 128° is obviously

FIG. 6.



Rates of polymerisation as a function of pressure at a series of temperatures.

FIG. 7.



Temperature coefficient of the rate of polymerisation at 50 mm. pressure of vinyl acetate ($T = ^\circ \text{K.}$).

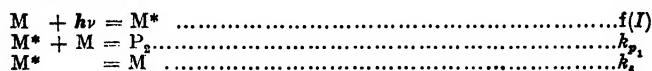
so far off the straight line as to indicate a complete change in mechanism which has not been further investigated. It being assumed that the energy of activation for the initiation process is negligible, this means that there is an energy of activation for the termination process and that it exceeds that of the propagation reactions for with mutual termination $E_{\text{app.}} = E_{\text{prop.}} - \frac{1}{2}E_{\text{term.}}$, where $E_{\text{prop.}}$ and $E_{\text{term.}}$ are the energies for propagation and termination, respectively. Only in the case of methyl acrylate has there been made a *minimum* value for $E_{\text{prop.}}$ and this amounts to 4000 cal. (Melville, *Proc. Roy. Soc.*, 1938, **A**, **167**, 99). Even if it is supposed that $E_{\text{prop.}}$ in the vinyl acetate reaction is 5000 cal., $E_{\text{term.}}$ amounts to about 20,000—a very high value indeed. In fact, considering the small concentration of active polymers, it would appear that the termination reaction would hardly ever occur in the gas phase at room temperature. There is here a peculiarity in a number of photo-gas-phase polymerisations which is kinetically not easily understandable. Yet with methyl acrylate if a strong inhibitor, e.g., oxygen or butadiene, is added to change completely the nature of the termination process the apparent temperature coefficient becomes positive, since a termination process normally requiring activation energy is replaced by one in which the energy of activation is practically zero. The phenomenon is not confined to gas-phase polymerisation, for in some liquid-phase polymerisations the chain length of the polymers decreases with increasing temperature, possibly owing to the energy of activation for termination exceeding that for propagation.

The critical limit. Before attempting to discuss the abnormal pressure dependence of this polymerisation the main kinetic features may be summarised as follows: (a) The rapid falling off in rate at low pressures and temperatures—the reaction being apparently normal at high temperatures and pressures. (b) Dependence of the “limit” on temperature. (c) Independence of limit on intensity and state of the tube, i.e., whether covered or not. (d) Termination mechanism of polymerisation not altered in the low-pressure, low-temperature region. (e) Limit apparently affected by *mode* of initiation.

The limit appears to have no connection with the explosion limit in other chain reactions, for the rate above the limit is in no sense indefinitely fast, the reaction being under complete control. The best proof of this suggestion is that the intensity exponent never falls below 0.5 whereas in an incipient explosion, e.g., in the $\text{H}_2\text{-N}_2\text{O-O}_2$ system sensitised by hydrogen atoms, the exponent may fall below the normal value of 0.5 when the reaction gets out of hand (Melville, *Proc. Roy. Soc.*, 1934, **A**, **146**, 737).

It would appear to be necessary to introduce some mechanism at low pressures which leads to a diminution in velocity rather than introduce some phenomenon which leads to an abnormal increase

in rate at high pressures as in gaseous explosions or in the polymerisation of methyl vinyl ketone (Jones and Melville, *ibid.*, 1946, A, 187, 19). All the above evidence indicates that neither termination nor propagation factors are affected and that therefore the phenomenon has something to do with the initiation process. The shift of the limit by changing from direct to sensitised initiation and the non-existence of the limit in the radical-sensitised reaction are additional certain pointers to this conclusion. It is probable that the primary photochemical efficiency is not high, *i.e.*, some of the energy absorbed by the vinyl acetate molecule is lost before another molecule of monomer can react with it. Thus we may have two competing processes:



As the pressure is reduced, a greater proportion of the M^* molecules lose their energy by some kind of a process not involving a collision with a monomer molecule. Mutual termination being assumed, then

$$d[\text{M}^*]/dt = f(I) - k_s[\text{M}^*] - k_{p_1}[\text{M}^*][\text{M}] = 0$$

and in general

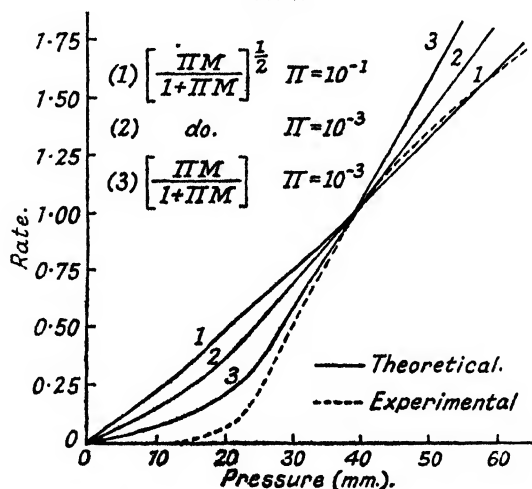
$$d[\text{P}_n]/dt = k_{p_{n-1}}[\text{P}_{n-1}][\text{M}] - k_{p_n}[\text{P}_n][\text{M}] - k_{t_n}[\text{P}_n]\Sigma k_{t_n}[\text{P}_n] = 0$$

Solving these equations in the usual way, we have

$$\begin{aligned} -d[\text{M}]/dt &= [\text{M}]\{f(I)\}^{\frac{1}{2}} \delta^{-1} \{k_s[\text{M}]/[k_s + k_{p_1}(\text{M})]\}^{\frac{1}{2}} \\ &= [\text{M}]f(I)^{\frac{1}{2}} \delta^{-1} \{\pi[\text{M}]/[1 + \pi(\text{M})]\}^{\frac{1}{2}} \end{aligned}$$

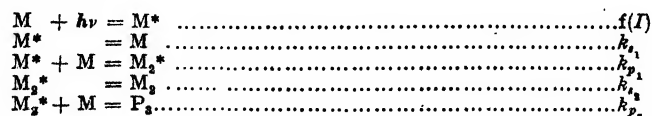
where $\pi = k_{p_1}/k_s$. At high values of $[\text{M}]$, this gives linear dependence of rate on $[\text{M}]$, but at low pressure the rate only varies as $[\text{M}]^{3/2}$ and would obviously not fall off quickly enough to be in accordance with experimental results. This is best shown by computing a value of π from experimental results. Assuming that the reaction is normal at 50 mm. and taking the rate at 24 mm., we have in the region of abnormality $R = 0.16$, $\pi = 3.0 \times 10^{-3}$ with $[\text{M}]$ in mm. At 20 mm. $\pi = 0.6 \times 10^{-3}$. Hence, taking a mean value of 10^{-3} and plotting the rate-pressure curve in Fig. 8 such that at one point, namely,

FIG. 8.



Relationship between theoretical and experimental curves, for the variation of rate with pressure.

40 mm., it is adjusted to coincide with the broken experimental curve, it will be seen that although the shape is approximately right the agreement both at low and at high pressures is such that the theory is not good enough to account for the observations. A better approximation may be obtained if it is assumed that not only the activated monomer but also the dimer may spontaneously lose its energy. Thus the scheme would be:



This leads to an expression

$$- \frac{d[\text{M}]}{dt} = [\text{M}] \delta^{-1} f(I)^{\frac{1}{2}} \left[\frac{k_{p_1}[\text{M}]}{k_s + k_{p_1}[\text{M}]} \right]^{\frac{1}{2}} \left[\frac{k_{p_2}[\text{M}]}{k_{p_2} + k_{p_3}[\text{M}]} \right]^{\frac{1}{2}}$$

If $k_p/k_t = k_{ps}/k_{is} = \pi$, which is a reasonable assumption, this simplifies to

$$-\frac{d[M]}{dt} = [M]\delta^{-1/2}(I)^{1/2} \left(\frac{\pi[M]}{1 + \pi[M]} \right)$$

and as will be seen from Fig. 8 gives a plot agreeing more closely with the results below 40 mm., although the high-pressure agreement is inferior. The intervention of this kind of deactivation process might be extended to higher active polymers, but it is evident that the process cannot extend indefinitely for it would constitute another way in which the active polymers are destroyed, whereas the intensity exponent clearly indicates mutual destruction of the active polymers. Although the above theory does not quantitatively account for the shape of the R - p curve, it is in accordance with the observations made in connection with the position of the so-called limit, namely, independence of intensity and of the state of the vessel. Since the limit depends on temperature, this means that π increases with increasing temperature. This is entirely in accordance with expectation; k_t , k_p are unlikely to be affected by temperature, since spontaneous loss of large amounts of energy is unlikely to be influenced by relatively small changes in energy; k_{ps} , on the other hand, is a propagation coefficient and will certainly increase with increasing temperature. The theory is not good enough to enable π or some similar parameter to be accurately computed, but an approximate estimate may be made in the following manner. Suppose there is no appreciable spontaneous deactivation at 40 mm. and the pressure p_1 is found from Fig. 8 at which the rate is half what it would have been in absence of this effect; then at this pressure the probabilities of propagation and deactivation are equal, and if p_1' and p_1'' are the pressures at two temperatures, the energy of activation of the propagation reaction will be given by

$$E_p = 4.57 \log_{10} \frac{p_1'}{p_1''} \frac{T_1 T_2}{(T_1 - T_2)}$$

where T_1 and T_2 are the corresponding temperatures. For 14° , $p_1' = 28$ mm. and at 45° $p_1'' = 22$ mm.; hence $E_p = 1400$ cals.

Nature of the Photopolymer.—The polymer deposited as a result of the photochemical reaction is insoluble—a drawback which prevents a direct measurement of the chain length of the reaction. In view of the small number of cross-links needed to render a polymer insoluble, it is not unreasonable to suppose that the reaction responsible for branching and the type of links involved in the process may be entirely different from those constituting the main bulk of the polymer. The polymer was therefore formed under carefully controlled conditions by running the experiment at a constant pressure of 30 mm. and 15° until about 0.6 g. of polymer was deposited. The polymer was then washed out of the reaction vessel with acetone, in which it swelled but did not dissolve. The resulting material was suspended in dry methyl alcohol and treated with methyl-alcoholic potassium hydroxide. The white suspension so obtained was poured into water, in which it was completely soluble. Hence, conversion of the polyvinyl acetate into polyvinyl alcohol resulted in a breakdown of the three-dimensional polymer, which points to the fact that a hydrolysable link is responsible for joining the primary chains of the polymer together.

Inhibition.—A study of the effect of inhibitors on a chain reaction throws much light on the mechanism of the reaction. As will be shown, this is particularly true with vinyl acetate where a variety of inhibitory mechanisms may operate. Oxygen and butadiene are both effective inhibitors but, surprisingly enough, chemically inert gases like argon, helium, and hydrogen also function as inhibitors.

Oxygen. According to the theory of polymerisation (Gee and Melville, *Trans. Faraday Soc.*, 1944, 40, 240) the expression for the rate of a completely inhibited reaction is

$$-d[M]/dt = [M]I(I)/\beta[O_2]$$

where $\beta = k_d/k_p$, k_d being the velocity coefficient for the interaction of inhibitor with active polymer. In order to get reliable results, the bracketing technique was employed for these experiments, *i.e.*, every run with the inhibitor present was preceded and followed by a run with pure vinyl acetate. With a pressure of 30 mm., the results of a series of runs are shown in Fig. 9, where reciprocal rate is plotted against oxygen pressure. In accordance with the theory, a straight line may be drawn through the points. Another result of inhibition of a reaction which is normally terminated by mutual destruction of the active polymers is that the intensity exponent should simultaneously increase from 0.5 to a value approaching 1.0 depending on the extent of the inhibition. A typical set of runs is given in Table II, the bracketing technique being employed and decrease of pressure being used for the measurement of rate.

TABLE II.

Vinyl acetate pressure, 31 mm. Temp. 20° .

Oxygen (mm.)	0	1.2	1.2	1.2	0
Intensity	1.00	1.00	0.125	1.00	1.00
Time (mins.) for pressure to fall 1 mm.	1.8	5.0	23.0	5.0	2.1

Intensity exponent = 0.74.

This increase of exponent to 0.74 clearly shows that inhibition is termination of growth of the polymer by the interaction of oxygen with it.

As will be shown in the following paper, it is possible to study the kinetics of the free-radical polymerisation below the critical limit, and thus in absence of the direct photopolymerisation. Table III shows that oxygen has no effect on the reaction initiated by methyl radicals and only a comparatively small effect on that initiated by hydrogen atoms, and this in spite of the fact that the rates of polymerisation are approximately the same as those in Table II. The fact that oxygen slightly inhibits the

TABLE III.

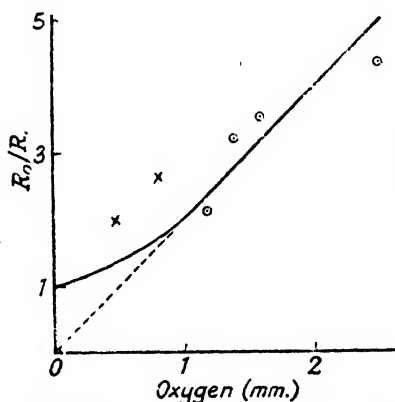
Effect of oxygen on free-radical-sensitised reaction at 20°.

Vinyl acetate press. (mm.).	Acetone (mm.).	Oxygen (mm.).	Rate (mm./min.).	Vinyl acetate.	Hydrogen.	Oxygen.	Rate.
Methyl radical reaction.				Hydrogen atom reaction.			
{ 17.3	45	0.1	0.217	14.3	43	—	0.45
{ 17.8	48	—	0.207	15.5	46	2.3	0.30
{ 16.7	53	3.2	0.240	14.7	48	—	0.42
{ 17.1	57	—	0.241				

hydrogen-atom reaction is quite possibly due to direct interaction of hydrogen atoms and oxygen molecules. The important point is that oxygen clearly discriminates between the two kinds of reaction.

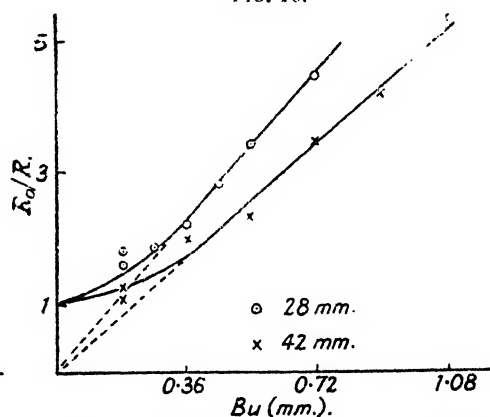
Butadiene. Butadiene is a more powerful inhibitor than oxygen and hence smaller pressures of the gas are needed. A gas pipette method was therefore adopted for introducing butadiene into the reaction system. The results at two vinyl acetate pressures are plotted in Fig. 10, in which the relative reciprocal rate is graphed against butadiene pressure. In these experiments bracketing methods were employed at all stages. Since in this case there is always the possibility of butadiene actually inter-polymerising with the vinyl acetate, with a resultant diminution in velocity, instead of acting as does oxygen, the variation of rate with intensity was measured. In the former case the square-root dependence would

FIG. 9.



Effect of oxygen in retarding polymerisation.

FIG. 10.



Effect of butadiene in retarding polymerisation, at 28 and 42 mm. of vinyl acetate.

still hold, while in the latter a linear dependence should be observed. The detailed results need not be given here except the following summary:

R_0/R	$R_{1.00}/R_{0.125}$	Exponent.	R_0/R	$R_{1.00}/R_{0.125}$	Exponent.	R_0/R	$R_{1.00}/R_{0.125}$	Exponent.
1.0	3.4	0.60	2.8	5.3	0.80	4.2	7.9	0.99

As the degree of inhibition (R_0/R) increases, the ratio of rates ($R_{1.00}/R_{0.125}$) at a fixed ratio of intensities likewise increases, corresponding to a general increase in intensity exponent. Additional confirmation is obtained in the following typical experiment with a vinyl acetate pressure of 33 mm. and butadiene 0.1 mm.: R_0/R at maximum intensity was 2.8, increasing to 3.9 at 0.125 of the maximum intensity. Thus, by reducing intensity and increasing thereby the chain length, the degree of inhibition is correspondingly increased. All these experiments conclusively show that when butadiene reacts with vinyl acetate active polymer it adds on and then the reaction stops. Normal molecules of vinyl acetate cannot react with a butadiene end of the polyvinyl acetate.

There is, however, one discrepancy. For the normal and the inhibited reaction we have respectively for the two rate equations:

$$-d[M]/dt = R_0 = [M]f(I)^{1/2}/\delta \text{ and } R = [M]f(I)/\beta[X]$$

Hence

$$R_0/R = \beta[X]/\delta f(I)^{1/2}$$

As seen above, this relationship is followed in regard to butadiene concentration and light intensity. It will be noted that the value of R_0/R is independent of R_0 and, more important, independent of $[M]$, yet in Fig. 10 the plots for two values of $[M]$ are not coincident. One possibility is that $f(I)^{1/2}$ depends on $[M]$ because of incomplete absorption of radiation. The slope of the R_0/R or $[X]$ curve would be less for higher values of $[M]$, which is in qualitative agreement with observation. The maximum change of slope in this case would be 1.2:1 whereas the observed value is 1.25:1. The linear dependence of R on $[M]$ at high enough temperatures would preclude this explanation. At lower pressures such as

28 mm., however, the vinyl acetate reaction begins to deviate quite markedly from normal behaviour. In order to get an expression for the reaction rate as a function of inhibitor concentration, an additional term, viz., $k_{sa}[P_n][X]$, is introduced into the differential equations defining $[P_n]$. This gives by the usual method

$$-d[M]/dt = [M]\{f(I) - k_{s_1}[P_1^*]\}/\beta[X]$$

But

$$[P_1^*] = f(I)/\{k_{s_1} + k_p[M] + k_{s_1}[X]\}$$

Therefore

$$-d[M]/dt = \frac{[M]f(I)}{[X]\beta} \left\{ \frac{k_{p_1}[M] + k_{s_1}[X]}{k_{s_1} + k_p[X] + k_{p_1}[M]} \right\}$$

Using the expression already obtained for the rate of reaction in absence of inhibitor, we have

$$R_0/R = \frac{\beta[X]}{\delta f(I)^{\frac{1}{2}}} \left\{ \frac{k_{p_1}[M]}{k_{p_1}[M] + k_{s_1}} \right\}^{\frac{1}{2}} \left\{ \frac{k_{s_1} + k_{p_1}[M] + k_{s_1}[X]}{k_{s_1}[X] + k_{p_1}[M]} \right\}$$

It has already been shown that $k_p/k_{s_1} \approx 10^{-3}$, hence $k_s \gg k_p[M]$ or $k_s[X]$ and

$$R_0/R = \frac{\beta k_{s_1}^{\frac{1}{2}}}{\delta f(I)^{\frac{1}{2}}} \cdot \frac{[M]^{\frac{1}{2}}[X]}{[M] + \beta^{-1}[X]}$$

Thus if $[M] \approx \beta^{-1}[X]$, decreasing values of $[M]$ will increase the slope of the R_0/R - $[X]$ curve.

Effect of Inert Gases.—Experiments with polymer-coated tubes seemed to indicate the existence of wall deactivation of the active polymer with clean or partly coated tubes. Thus it might be expected that the decrease in diffusion coefficient effected by the addition of inert gas might accelerate the polymerisation rate. When the experiment was done, precisely the opposite effect was obtained, a marked inhibition being observed. At first sight, this phenomenon is difficult to explain, since it is inconceivable that gases like argon, helium, and hydrogen could effect any chemical change in the active polymer that would lead to deactivation. As will be shown, inhibition does not occur by the termination of growth of the chains but is due to deactivation of excited molecules in the very early stages of polymerisation. This effect, indeed, is not then so unexpected in view of the abnormal pressure dependence of reaction and, in fact, provides further support for the hypothesis advanced to explain the occurrence of an apparent critical limiting pressure. Thus we have the curious phenomenon that inhibition by inert gases leads to an *increase* in chain length of the polymer and not a decrease as is usually the case.

The argon was obtained from a cylinder of the gas and was oxygen free. The helium was purified from more condensable gases by repeated treatment with active charcoal.

The results with argon for a series of vinyl acetate pressures are shown in Fig. 11. R_0/R and also $(R_0/R)^2$ are plotted against argon pressure. It is difficult to say which relationship is the better approximation, but one observation is important. Unlike those for oxygen and butadiene, these lines do not go through the origin but make an intercept of unity in the R_0/R axis. This at once shows that a different kind of inhibition comes into operation apart altogether from the fact that very much higher pressures are needed for inhibition to be observed. This is completely confirmed by measuring the intensity exponent. With a vinyl acetate pressure of 40 mm. and an argon pressure of 67 mm., $R_0/R = 2$, the intensity exponent is 0.60, the same value being obtained in the uninhibited reaction. This evidence certainly points to inhibition occurring in the initial stages of the reaction. Since the theory of the critical limit postulates the existence of an excited monomer which does not necessarily add on another molecule of monomer but may spontaneously lose its energy, probably by some internal rearrangement (it is hardly likely that chemical decomposition occurs, since it was earlier shown that decomposition seems to be an independent process brought about by short wave-lengths), it is natural to suppose that deactivation can also be brought about by collision with another molecule which facilitates this rearrangement or removes some of the energy from the excited molecule. In the expression for the value of $[P_1]$ another term has therefore to be added and the appropriate equation becomes

$$d[P_1]/dt = f(I) - k_{p_1}[P_1^*][M] - k_{s_1}[P_1^*] - k_{A_1}[P_1^*][A] = 0$$

Hence

$$R_0 = [M]\delta^{-\frac{1}{2}}f(I)^{\frac{1}{2}}\{k_{p_1}[M]/k_{s_1} + k_{p_1}[M]\}^{\frac{1}{2}}$$

and

$$R = [M]\delta^{-\frac{1}{2}}f(I)^{\frac{1}{2}}\{k_{p_1}[M]/(k_{p_1}[M] + k_{s_1} + k_{A_1}[A])\}^{\frac{1}{2}}$$

Therefore

$$R_0/R = \left\{ 1 + \frac{k_{A_1}[A]}{k_{s_1} + k_{p_1}[M]} \right\}^{\frac{1}{2}}$$

If argon deactivation is extended to P_2^* and we assume that $k_{p_1} : k_{s_1} : k_{A_1} = k_{p_2} : k_{s_2} : k_{A_2}$, then

$$R_0/R = 1 + k_{A_1}[A]/(k_{s_1} + k_{p_1}[M])$$

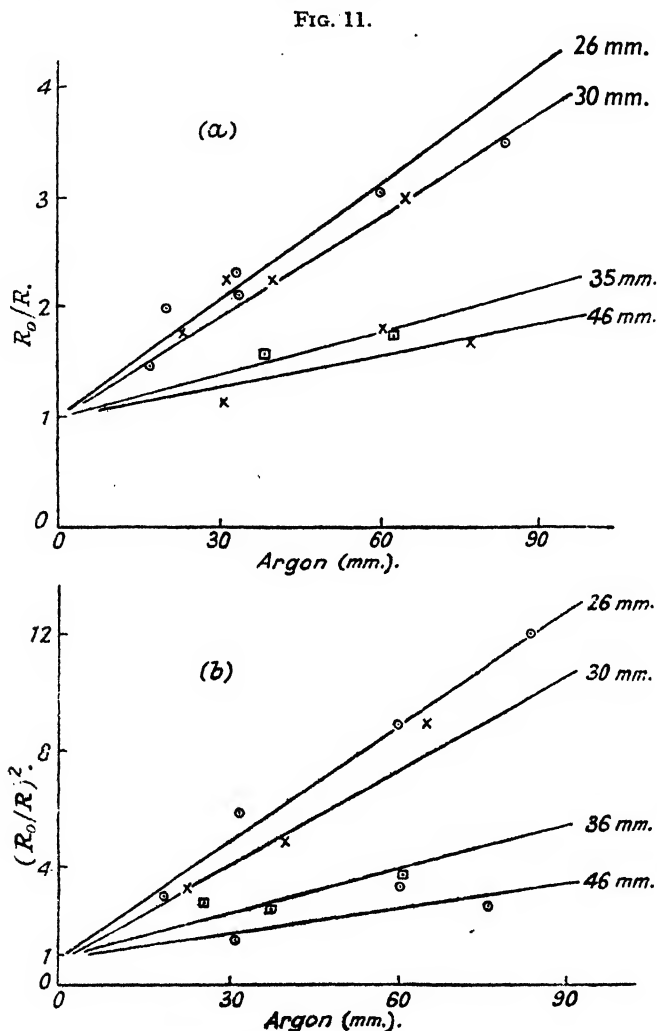
Rearranging these expressions, we have

$$\{(R_0/R)^2 - 1\}^{-1} = \frac{k_{s_1}}{k_{A_1}[A]} + \frac{k_p}{k_{A_1}[A]}[M]$$

$$(R_0/R)^2 - 1 = k_{A_1}[A]/k_{s_1} + k_{p_1}[M] \text{ and } R_0/R - 1 = k_{A_1}[A]/(k_{s_1} + k_{p_1}[M])$$

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Fig. 11 shows that a linear plot of R_0/R against argon pressure is obtained, and that the slopes of the lines are inversely proportional to the pressure of vinyl acetate. The intercept on the ordinate does not vary with argon pressure. This is not unexpected in view of the close approach to the critical limit when such relationships will break down. Experimentally it is difficult to decide between these two mechanisms.



Effect of argon in retarding the rate of polymerisation at various vinyl acetate pressures indicated. Figs. 11a and 11b show alternative ways of plotting the results.

Helium and hydrogen function in a similar manner, the intensity exponent not being affected when inhibition takes place. According to the above theory, the relative efficiencies of these gases can be obtained by plotting $(R_0/R)^2$ against the pressure of inert gas for a given vinyl acetate pressure. The relative slopes of these lines give the ratio of collision efficiencies $A : \text{He} : \text{H}_2 = 1 : 0.6 : 0.5$. If allowance is made for the different speeds, the collision efficiencies have the following values relative to argon: $\text{He } 0.085$, $\text{H}_2 \ 0.036$. In passing it is worth noting that inert gases have absolutely no effect on the free-radical polymerisation.

227. Radical-sensitised Polymerisation of Vinyl Acetate Vapour.

By H. W. MELVILLE and R. F. TUCKETT.

The kinetics of the polymerisation of vinyl acetate vapour initiated by hydrogen atoms and by methyl radicals has been investigated, with the following results. Owing to the fact that the direct photochemical polymerisation does not occur at room temperatures below 20 mm., the free-radical reaction can be studied alone by working at pressures below this limit. The reaction rate is proportional to the first power of the vinyl acetate pressure and to the square-root of the rate of production of radicals. The kinetic chain length of the reaction has been measured by the method of end-group analysis. The reaction has a high negative temperature coefficient.

These results show that the direct photo-reaction also proceeds by means of a radical mechanism, the correlation between the two reactions being close. The direct reaction initially involves the production of di-radicals which are subject to deactivation spontaneously or by collision with inert added gases. These gas-phase reactions exhibit the so-called gel effect to a maximum degree and thus the termination velocity coefficients are reduced to small values. This gives rise to overall apparent negative energies of activation.

In the previous paper it has been shown that vinyl acetate does not apparently undergo photochemical polymerisation at room temperature at pressures below 20 mm. In this respect it is unique but the phenomenon can be put to good use in the following way. With some molecules, *e.g.*, methyl methacrylate, it is comparatively easy to study the kinetics of the free-radical polymerisation without complications arising out of the occurrence of the direct photo-reaction; with other molecules like methyl acrylate this cannot conveniently be done for a variety of reasons. It is, however, important to study the kinetics of the radical reaction and thus characterise the type of polymerisation for purposes of reference so that by comparison it is possible to say whether or not the direct reaction, for example, goes by way of free radicals. At pressures below 20 mm. it proves to be possible to induce radical polymerisation and to study it to the complete exclusion of the direct reaction. The present paper describes the results obtained in this way.

The apparatus used was identical with that described in the previous paper. Special methods and modifications are described in the appropriate places.

Hydrogen-atom-sensitised Reaction.—Although molecular hydrogen is an inhibitor for the direct photo-polymerisation, it indirectly becomes a sensitiser if mercury vapour is present and instead of a high-pressure mercury lamp a low-pressure type emitting unreversed 2537 Å. radiation is employed. This phenomenon is well marked below the limiting pressure where, of course, no direct reaction can be detected. There is no doubt the accelerating effect of hydrogen is due to its sensitised dissociation to atomic hydrogen, which adds on to vinyl acetate to give a free radical, thus initiating polymerisation. There are some complications in the use of this indirect method. Excited mercury atoms will be deactivated by vinyl acetate molecules as well as by hydrogen and thereby start off a mercury-sensitised polymerisation, as has been shown in the previous paper. Fortunately, there is a pressure limit to this reaction (below) and hence its contribution to the total observed rate of polymerisation can easily be eliminated. Even at low pressures, mercury atoms will still be deactivated by vinyl acetate. The fraction f_{H_2} of excited mercury atoms deactivated by hydrogen molecules is simply given by

$$f_{H_2} = \frac{\sigma_{H_2}^2 [H_2] \mu_{H_2-Hg}^{-1}}{\sigma_{H_2}^2 [H_2] \mu_{H_2-Hg}^{-1} + \sigma_{VA}^2 [VA] \mu_{VA-Hg}^{-1}}$$

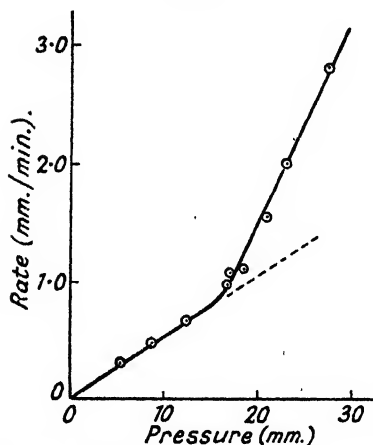
where σ is the sum of the quenching radii and μ is the reduced mass of the pairs of molecules concerned; $\sigma_{H_2}^2 = 6.0 \times 10^{-16}$ cm.² and σ_{VA}^2 is not known: it is probably about 20×10^{-16} cm.², for methyl methacrylate, for example, has $\sigma^2 = 25 \times 10^{-16}$ cm.² (Bolland, unpublished experiments). This value being taken, it is calculated that $f_{H_2} = 0.8$ for $H_2 : VA = 2.3 : 1$, and $f_{H_2} = 0.9$ for $H_2 : VA = 5.8 : 1$. Consequently, high hydrogen pressures were invariably used to eliminate complication of the kinetics in the above manner. The reproducibility of the free-radical reaction is much better than that of the direct photo-reaction, mainly because of the shorter chain lengths involved. Although the rate of reaction does not immediately attain its maximum value in a clean tube, a very light coating suffices to prevent completely any wall termination. Corrections due to absorption of monomer by polymer are practically absent.

The mixtures of hydrogen and vinyl acetate were prepared in two ways. In one procedure the reaction vessel was filled with vinyl acetate to a given pressure. This was condensed out, the side tube cooled in liquid air, and then hydrogen admitted. In the second procedure vinyl

acetate was admitted first, followed by hydrogen, the pressure of which was maintained at a high value in its reservoir so that little if any vinyl acetate vapour could diffuse out into the hydrogen reservoir. The former method was the more convenient where it was necessary to measure accurately the initial pressure of the hydrogen rather than the total pressure of the mixture.

A pressure of 30 mm. of hydrogen being used, the variation of initial rate of polymerisation with pressure of vinyl acetate is shown in Fig. 1. In the first place it will be seen there is a

FIG. 1.



Variation of total rate of polymerisation with vinyl acetate pressure.

marked acceleration in presence of hydrogen which can only occur because of the free-radical reaction induced by atomic hydrogen. Secondly, quite a fast reaction occurs at vinyl acetate pressures when the mercury-sensitised polymerisation of vinyl acetate does not proceed at all. At a pressure of 15 mm., however, this type of reaction seems to proceed in parallel with the hydrogen atom sensitised reaction. Below 15 mm. the free-radical reaction rate is proportional to the first power of the concentration of the acetate. Fig. 2 is a plot of the log of this rate as a function of radiation intensity. The slope of the line is 0.7, showing that quite a large proportion of the free radicals combines in the gas phase. Thus the kinetics are approximately expressed simply by

$$-d[M]/dt = \text{const. } [M]^{1/2}$$

characteristic of a normal reaction in which mutual termination occurs and in which the rate of initiation is independent of monomer concentration. When individual runs are examined, however, and allowance is made for the disappearance of the appropriate amount of hydrogen, the first-order "constant" decreases with decreasing pressure as shown in Table I. Even a second-order "constant" exhibits a slight tendency to decrease. It is evident that this

TABLE I.

Temp. 15°. Hydrogen pressure 27.2 mm.

Time (mins.)	0.	1.	2.	3.5	5.	7.	9.	10.
Press. (mm.) of vinyl acetate, uncorr.	18.6	15.5	13.1	10.9	9.5	8.1	7.0	6.5
Press. (mm.) of vinyl acetate, corr. for loss of H ₂	18.6	15.6	13.4	11.4	10.3	9.2	8.4	8.1
k (min. ⁻¹) (1st order)	—	0.177	0.164	0.140	0.118	0.100	0.088	0.083
k (min. ⁻¹ mm. ⁻¹) (2nd order)...	—	0.0100	0.0105	0.0095	0.0086	0.0079	0.0072	0.0070

diminution in velocity must be due to the accumulation of some rate-retarding molecule produced as a result of secondary reactions.

The addition of hydrogen actually inhibits the mercury photosensitised polymerisation since the hydrogen molecule deactivates quite a proportion of the excited mercury atoms. In fact it is possible to obtain an approximate estimate of the quenching radius of the vinyl acetate molecules from such data. Table II gives the relevant data for low vinyl acetate pressures.

TABLE II.

Monomer pressure (mm.)	18.0	22.3
Rate of mercury-sensitised reaction	0.9	2.2
Total rate of reaction with 30 mm. of hydrogen	1.00	1.85
Estimated rate of Hg-sensitised reaction in presence of hydrogen	0.79	0.66
Fraction of H ₂ molecules deactivating excited Hg atoms (f _{H₂})	0.79	0.69

At a pressure of 18.0 mm. the mercury-sensitised rate is reduced from 0.9 to 0.19 mm./min., since a fraction f_{H_2} of the mercury atoms is deactivated by hydrogen. The value of f_{H_2} at 22.3 mm. is 0.69. But f_{H_2} is given by the equation

$$f_{H_2} = \frac{\sigma_{H_2}[H_2]/[VA] \cdot \mu_{H_2-Hg}^{1/2}}{\sigma_{H_2}[H_2]/[VA]\mu_{H_2-Hg}^{1/2} + \sigma_{VA}^2\mu_{H_2-Hg}^{1/2}}$$

If σ_{H_2} is taken as 6.0×10^{-16} mm.², then since $[H_2]/[VA]$ is known, σ_{VA-H_2} may be computed. The figures are 20 and 25×10^{-16} mm.², respectively, in good agreement with the experimentally determined value of 25×10^{-16} mm.² for methyl methacrylate.

Inhibitors.—Although an examination of the course of an individual run showed unmistakable evidence of the production of an inhibitor, more direct evidence was desirable. This was obtained in the following manner. Unfortunately, the constant pressure-variable volume method cannot be used, but a modification is possible. A mixture of monomer and hydrogen at a suitable pressure is irradiated for such a time that 2 mm. of vinyl acetate are polymerised. The gases are then thoroughly mixed by moving the mercury in the gas burette, and the pressure is adjusted so that the original vinyl acetate pressure is obtained. Next, another 2 mm. of vinyl acetate are polymerised and the time is noted. If no inhibitor had been produced the

FIG. 2.

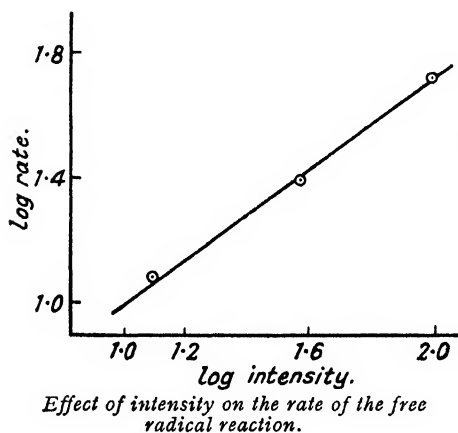
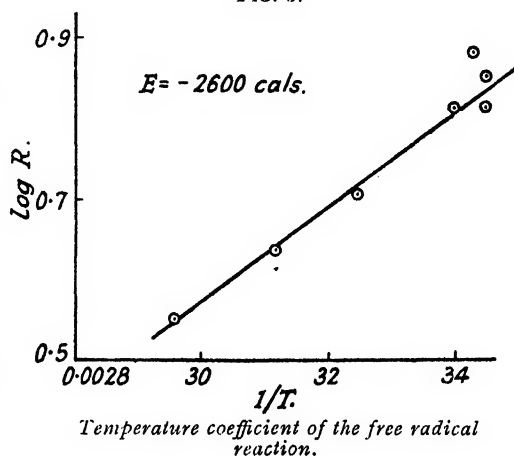


FIG. 3.



time should have been slightly shorter because of the slight diminution in volume of the system. Table III shows that, in fact, these times for 2 mm. polymerisation increased continually.

TABLE III.

	Vinyl acetate 18.8 mm.				Hydrogen 24.2 mm.			
Initial vol. of system (c.c.) ...	210	198	187	176	167	159	150	
Time (mins.) for $-\Delta p = 2$ mm.	1.23	1.18	1.63	2.58	3.50	4.75	6.75	

Further conclusive proof of the presence of an inhibitor can be obtained by examining the intensity exponent, which should increase as inhibitor accumulates. This is best done by carrying out two runs with different intensities and comparing the ratio of times required for the same pressure decrease throughout the course of the reaction. The following results were obtained in two such runs.

Ratio of intensities 8.0 : 1. Vinyl acetate 19.0 mm. Hydrogen 27.5 mm.			
Pressure range (mm.)	18—11	6.0—3.5	4.5—3.5
Ratio of times	2.3	3.16	3.8

The increase in ratio shows that the exponent is increasing from about 0.5 towards unity at the end of the run.

The inhibitor is not produced by short-wave radiations from the 2537 Å. lamp, for an acetic acid filter does not cut down inhibitor production. It is condensable in liquid air and solid carbon dioxide. This was shown by condensing the contents of the reaction vessel after a run into a suitable trap and pumping off all non-condensable gas. Fresh hydrogen was then added, and the run continued. At -183° and -80° the inhibitor was retained in the trap.

Temperature Coefficient.—The temperature coefficient of the free-radical reaction can only be studied over a comparatively small range since at higher temperatures the direct reaction begins to make its appearance and thus complicates the interpretation of the kinetics. Fig. 3 shows how the rate varies with temperature, the rate being measured by taking the reciprocal of the time for the pressure of vinyl acetate to fall 4 mm. It will be seen that the temperature

coefficient is negative, with a value of -2600 cal. So far as is known, the addition of atomic hydrogen to an unsaturated molecule proceeds with such a small energy of activation that the temperature coefficient of the polymerisation process must certainly be due to that of the propagation and termination reactions. Since the polymerisation ends by mutual destruction of active molecules, the apparent energy of activation is equal to $E_p - \frac{1}{2}E_T$, E_p and E_T being the energies of activation for propagation and termination. These temperature coefficients were measured at different intensities and the results are given in Table IV.

TABLE IV.
Chain length at 17° :

8.		12.		50.	
Temp.	τ (mins.) for $\Delta p = 4$ mm.	Temp.	τ (mins.) for $\Delta p = 4$ mm.	Temp.	τ (mins.) for $\Delta p = 4$ mm.
17.5°	4.00	17.0°	6.25	18.0°	10.0
19.5	3.6	18.6	5.3	19.0	11.4
25.0	5.2	21.3	6.2	32.0	19.7
35.5	4.3	34.5	7.9	48.0	38.4
55.0	5.5	47.6	9.3	—	—
—	—	65.0	11.2	—	—
$E = -1900$ cal.		$E = -2600$ cal.		$E = -8200$ cal.	

This reaction thus falls into line with the direct photo-polymerisation and with the polymerisation of methyl acrylate and of methyl vinyl ketone in the gas phase in that negative energies of activation are observed. With the free-radical reaction it is probable that the value would not change with further increase in chain length. The mere fact that the value is negative would imply that E_T is greater than E_p by a substantial amount. This fact is anomalous since it would imply that the two free radicals must become activated before they react with each other; in other words, more activation energy is required for the interaction of two radicals than is required for the interaction between a radical and a double bond. Such a state of affairs is hardly conceivable, but there appears to be no valid alternative explanation. The variation of the apparent energy of activation with chain length may quite well be due to a variation in E_p or E_T , especially when the chain length is so short.

Chain Length.—If after a hydrogen-atom-sensitised polymerisation all the vinyl acetate vapour is condensed out by passing the mixture through a trap cooled in liquid air, the hydrogen pressure is less than that at the start of the run. For example, with 18.6 mm. of vinyl acetate and 27.15 mm. of hydrogen a time of illumination of 10 mins. gives a total pressure decrease of 12.3 mm., the hydrogen pressure being now 25.85 mm. The reason for the small fall in pressure is that the hydrogen atom responsible for starting polymerisation is incorporated in the polymer itself. Thus the decrease may be made the basis of measuring the kinetic chain length of the reaction and therefore the number average molecular weight of the polymer.

Owing to the small pressure decrease certain precautions have to be taken. Only tubes lightly coated with polymer may be used since atomic hydrogen may reduce the polymer and so be removed in a non-polymerisation reaction. The most convenient method of measuring the decrease in hydrogen pressure consists in admitting the appropriate amount of vinyl acetate, freezing this out, and then admitting hydrogen. After the run the vinyl acetate is once more frozen out, and the hydrogen pressure measured. After correction for the cooling of the trap, the decrease in pressure of hydrogen is subtracted from the total observed pressure decrease to give the diminution in vinyl acetate pressure.

In considering the kinetics of the reaction as a whole it is necessary first to determine whether there is any possibility of a hydrogen atom terminating polymerisation as well as starting it. If this kind of termination occurred exclusively, then it can be shown (Melville, *Proc. Roy. Soc.*, 1937, *A*, 163, 511) that $R \sim \text{const.} [M]^2$, the rate being independent of intensity. Since the observed kinetics are $R \sim \text{const.} [M]I^{\frac{1}{2}}$, it is evident that this kind of termination does not enter into the question. As has been seen in Table IV, the kinetic chain length is comparatively short, and this introduces a slight complication. The general expression for the concentration of the active polymer is

$$d[P]/dt = I - k_t[P]^2 = 0$$

where $I = k[H][M]$, k being the bimolecular coefficient for the reaction of hydrogen atoms with the monomer. For short chains, then

$$-d[M]/dt = I + I^{\frac{1}{2}}[M]k_p/k_t$$

Thus the rate will not be strictly proportional to the square-root of the intensity. The deviation may be computed in the following way. Suppose $-d[M]/dt \sim I^x$; then for two intensities

$$x = [\log R_2/R_1]/[\log (I_2/I_1)]$$

Let $I_2/I_1 = 8$, as was used in some experiments, then, if $\delta = k_t/k_p$,

$$\begin{aligned} x \log 8 &= \log \frac{I_2 + [M]\delta^{-1}I_2^{\frac{1}{2}}}{I_1 + [M]\delta^{-1}I_1^{\frac{1}{2}}} \\ &= \log \sqrt{8} + \log \frac{v_2}{v_2 - 0.65} \end{aligned}$$

where v_2 is the chain length at intensity I_2 ; or

$$x = 0.50 + 1.11 \log v_2/(v_2 - 0.65)$$

Hence x may be obtained for various different values of v_2 as follows :

$v_2 =$	4	5	6	12	∞
$x =$	0.586	0.567	0.55	0.53	0.500

For example, with a vinyl acetate pressure of 19 mm. and $H_2 = 27.5$ mm. at 17° , the chain length is greater than 10 for full intensity and over 30 at the 0.125 full intensity x (experimental) = 0.47.

Independent evidence also indicates mutual termination of polymer growth. In such a mechanism the chain length should be inversely proportional to the square-root of the intensity of incident light. Instantaneous values of the chain length cannot, of course, be computed because of the impossibility of measuring accurately small decreases in hydrogen pressure; hence the following procedure was adopted. The hydrogen-vinyl acetate mixture is illuminated, and the chain length measured by the above-mentioned method. A second measurement is made by resuming the run. In this way the corrected vinyl acetate pressure-time curve is constructed. The rate of polymerisation at say two given pressures can then be read off. The rate of hydrogen loss is assumed to be the average rate of loss over the run. The whole procedure is then repeated at a lower intensity. The results in Table V show the expected dependence of chain length on intensity, and the observed figures are in reasonably good agreement with the theoretical values calculated from the ratio of the intensities.

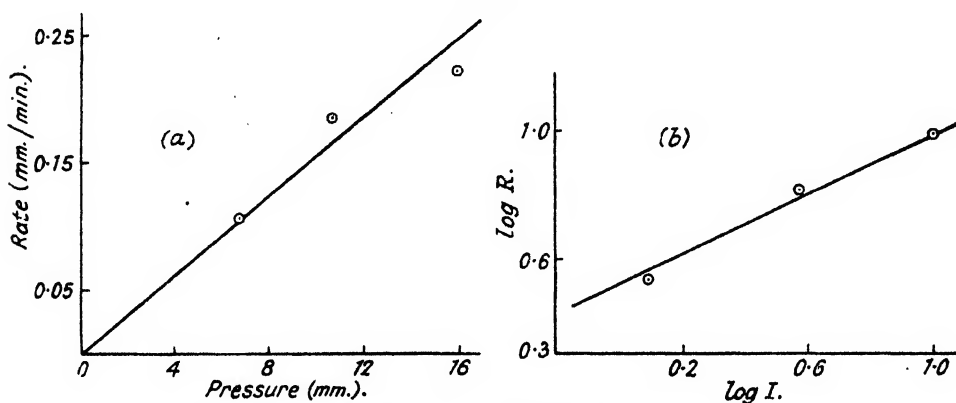
TABLE V.

Intensity.	Chain length at vinyl acetate pressures (mm.) of :		Ratio of chain lengths obs. at vinyl acetate pressures (mm.) of :		Calculated ratio of chain lengths.
—	13.0	6.0	13.0	6.0	—
1.00	13.5	2.7	3.6	2.5	2.83
0.125	49	6.8	—	—	—

Methyl-radical-sensitised Reaction.—Hydrogen atoms are not always the most suitable type of initiator for a free-radical reaction. In addition, it has been shown with butadiene, for example (Jones and Melville, *Proc. Roy. Soc.*, 1946, A, **187**, 87), that whereas methyl radicals initiate polymerisation, hydrogen atoms lead to hydrogenation of the butadiene. It was therefore desirable to see whether methyl radicals from photodecomposing acetone could effect polymerisation of vinyl acetate vapour and so find whether the kinetics of the two reactions are identical. With acetone as a source of methyl radicals there is a very marked acceleration of polymerisation, for at 22 mm. vinyl acetate pressure the rate was 0.02 mm./min. but on addition of 40 mm. of acetone the rate jumped to 0.45 mm./min. Even well below the critical limit with VA = 16 mm., the rate was 0.22 mm./min., the rate of the direct reaction being negligible. In Fig. 4 the kinetics are briefly summarised. In Fig. 4(a) it will be seen that the rate is proportional to pressure, the upper limit of pressure being fixed by the limit for the direct reaction. In Fig. 4(b) log rate is plotted against log intensity. The slope of the straight line is 0.46. Thus the kinetics of the hydrogen-atom- and of the methyl-radical-sensitised reaction are exactly similar. There is, however, a further interest in this similarity. If matters are so adjusted that the two reactions occur at the same speed, then the chain length must be identical and the rate of initiation must also be identical. But the rate of production of hydrogen atoms is known, and hence it should in principle be possible to measure the rate of production of methyl radicals from acetone, and thus throw some further light on the photochemistry of this molecule. Much has already been written about the photochemistry

of acetone, and it is usually presumed that when the molecule does dissociate the first act is the production of acetyl and methyl radicals and that the former subsequently decompose to methyl and carbon monoxide, though under some conditions they may combine to diacetyl. In a recent paper evidence is presented to show that apparently the excited acetone molecule may decompose to fragments of ethane and carbon monoxide *without* the production of radicals. The production of acetyl does complicate matters. In some acetone-catalysed polymerisations (Jones and Melville, *loc. cit.*) it has been found that the rate of production of carbon monoxide from acetone is diminished when monomer is present. This would imply that the acetyl radical reacts with the monomer before it has time to decompose. Similar experiments were made with acetone and vinyl acetate, pressures of 16–17 mm. of vinyl acetate and 35.40 mm. of acetone being used; thus, in 5 mins. 11.7×10^{-3} mm. of carbon monoxide were produced with acetone alone; with vinyl acetate present, 4.6 mm. of gas were polymerised and the pressure of monoxide was 11.2×10^{-3} mm. In another series of experiments, carbon monoxide production was 29×10^{-3} and 28×10^{-3} mm., respectively, in presence and in absence of vinyl acetate. Thus acetyl radicals do not initiate polymerisation, unless, of course, the carbon monoxide molecule is eliminated just when the acetyl radical meets a vinyl acetate molecule, an unlikely state of affairs.

FIG. 4.



(a) Effect of pressure on the methyl-radical-sensitised reaction.

(b) Effect of intensity on the radical-sensitised reaction.

The experimental procedure is somewhat complicated. First of all two lamps are used, the first a low-pressure lamp emitting the 2537 Å. line to dissociate the hydrogen, the second a high-pressure lamp to dissociate the acetone. The distances of these lamps from the reaction vessel are so adjusted that with a given acetone pressure the rates of polymerisation are the same. First, a hydrogen atom run is made, the chain length being measured at two points. Next another hydrogen atom run is made for approximately half the period, and the chain length re-measured. Acetone is then admitted to a pressure of 50 mm. The hydrogen pressure is then measured again since a small amount escapes on introduction of the acetone. The hydrogen-vinyl acetate-acetone mixture is then irradiated with the high-pressure lamp for a time such that polymerisation occurs to the same extent as with the first hydrogen atom run. The data from the first run then give the hydrogen molecule consumption during the second part of the run. Finally, the vinyl acetate and acetone are condensed out, and the total pressure due to hydrogen and to carbon monoxide is measured.

By this method it was found over the same range of vinyl acetate pressures, *viz.*, 17.5–12.5 mm., that the carbon monoxide produced from the photodecomposing acetone was equal to volume of hydrogen consumed in the corresponding part of the hydrogen run. The data for a run of this type are given below.

Vinyl acetate = 22.0 mm. Hydrogen 35.0 mm. Acetone 50.0 mm.

Type of run.	Rate of 1st half of polymerisation.	Rate of 2nd half of polymerisation.	
Me	1.38	0.80	0.25 mm. CO produced
H	1.32	0.73	0.30 mm. H ₂ consumed
Me	1.46	0.98	0.25 mm. CO produced

General Discussion of the Vinyl Acetate Reaction.

It now remains to discuss and compare the free-radical and the direct polymerisation reactions. The former is at first sight the simpler, for the mechanism consists in the addition of the hydrogen atom or methyl radical to the vinyl acetate molecule to form another free radical, to which are subsequently added further vinyl acetate molecules until two of these comparatively large free radicals interact. It is not yet certain whether this results in combination or disproportionation. The anomalous feature of this and other gas-phase reactions is the negative temperature coefficient. This may be due to a variety of factors. First, even if the radical polymers are small, it may be that in course of growth a new solid phase appears with the consequence that monomer will presumably be adsorbed on this growing particle as a necessary preliminary to addition. The rate of polymerisation will then be proportional to the concentration of monomer in the polymer particle. Increase of temperature will consequently decrease this concentration so that this factor alone will give rise to an apparent negative temperature coefficient. Second, quite a different factor may also give rise to a diminished temperature coefficient. It has now been established (Burnett and Melville, *Nature*, 1946, 158, 553) that when polymerisation of vinyl acetate occurs in a solvent such as hexane in which the polymer is not very soluble, the effect of precipitating out the growing polymer is to diminish the magnitude of the bimolecular reaction coefficient for the termination of polymer growth. The coefficient which is not normally affected by temperature acquires in these circumstances a positive temperature coefficient. A similar precipitation will occur even more readily in the gas phase. It is not therefore surprising that an overall negative temperature coefficient is observed, and that the larger the kinetic chain length the higher the value of the negative energy of activation. It is possible that both factors operate together.

With the direct reaction at sufficiently high pressures, the general kinetics are similar to those of the pure radical reaction. For comparable rates of initiation the overall polymerisation velocities of the radical and of the direct reaction are quite similar. It would therefore seem probable that the direct reaction also proceeds by a free-radical mechanism. The problem then is to understand why the critical pressure limit and inert gas effects make their appearance. The matter is most satisfactorily accounted for if it is assumed that absorption of ultra-violet light by monomer results in the production of a di-radical. Such a radical is simply an electronically excited molecule. The results show clearly that such a molecule can spontaneously give up its electronic energy or give it up to an inert gas at quite low pressures. At high enough pressures, however, further monomer molecules will add on to both ends of this di-radical. It is unfortunate that the photopolymer is made insoluble by some secondary reactions and thus its molecular weight cannot be compared with that of the free-radical polymer. The negative temperature coefficient of the direct reaction then is explained in a similar manner to that of the radical reaction.

Experimental evidence has been given elsewhere to suggest that the polymerisation of vinyl acetate in the liquid phase or in solution goes by way of free radicals. Here there should be an exact correlation between the reaction in the two phases. The obstacle to establishing a numerical correlation is due wholly to the so-called gel effect, *i.e.*, to the influence of environment or polymer shape on the velocity coefficient for the termination of molecular growth. In the liquid phase precisely similar overall kinetics are observed, but it is evident that the magnitudes of the velocity coefficients cannot be compared. For the gas phase the termination coefficient will not have its maximum value but some lower and ill-defined value. For these reasons the liquid-phase reaction with either pure monomer or monomer in a good solvent is far simpler than the gas-phase reaction.

The experiments described in this and the preceding paper were carried out in 1938–39 in the Colloid Science Department, The University, Cambridge. We should like to thank Professor E. K. Rideal for his great encouragement and interest in this work. These researches were made possible owing to the generosity of Aero Research Limited, Duxford, Cambridgeshire, who kindly provided a maintenance grant to one of us (R. F. T.).

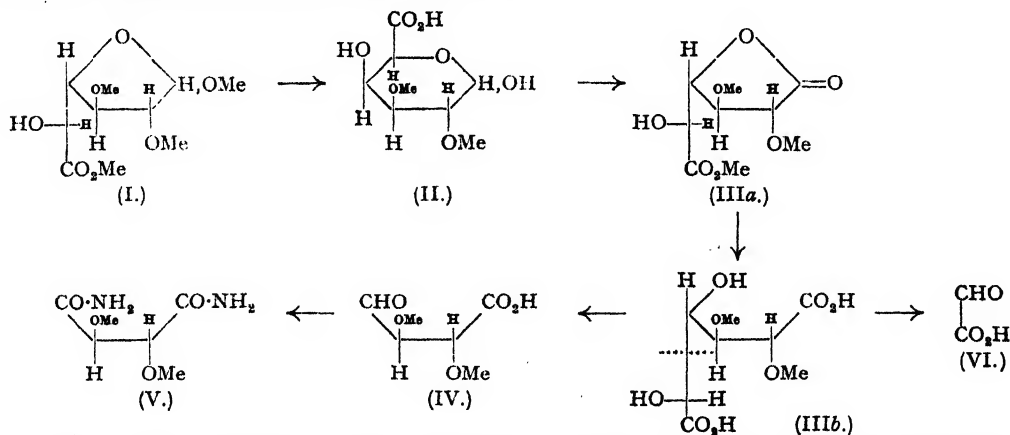
228. Pectic Substances. Part V. The Molecular Structure of Strawberry and Apple Pectic Acids.

By G. H. BEAVAN and J. K. N. JONES.

Degradation products prepared from strawberry pectin and apple pectin by boiling with methanolic hydrogen chloride have been converted into their methylated derivatives. Hydrolysis of the latter with methanolic hydrogen chloride yielded the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside as the main product. The bearing of these observations on the chemical structure of pectic acid is discussed.

PECTINS commonly occur in fruit and have been the subject of chemical investigation by many workers, and it is now generally accepted that they are mixtures of polysaccharides, amongst which galactan, araban, and polygalacturonosides predominate (for a review of the evidence see the article by Hirst and Jones, "Advances in Carbohydrate Chemistry", Vol. II, 1946). These polysaccharides are in close physical union, and great difficulty is experienced in separating the components in a pure condition, particularly those of the polygalacturonoside fraction. Arabans from peanut, apple, and citrus pectins have been shown to consist of *l*-arabofuranose residues linked to form a branched chain polymer (Hirst and Jones, *J.*, 1938, 496; 1939, 453, 454; Beavan, Hirst, and Jones, *J.*, 1939, 1865), whilst the galactan from *Lupinus albus* consists of β -*d*-galactopyranose residues in the form of a linear polymer (Hirst, Jones, and Walder, *J.*, forthcoming publications). These two polysaccharides could not therefore be derived one from the other by oxidation and decarboxylation at C₆ of the pyranose residues. In view of these results it became of special interest to determine whether any correlation exists between the structures of the pectic acid and of either of the polysaccharides associated with it, and whether pectic acids from different sources possess similar structures.

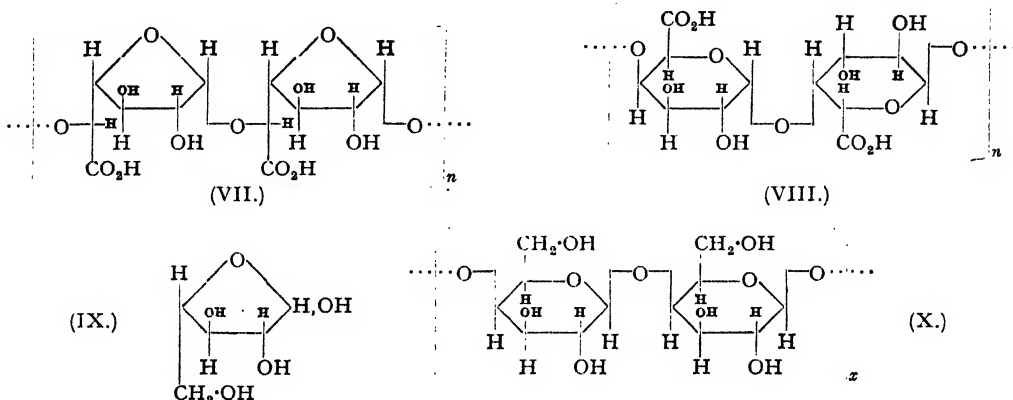
The investigation of the pectic acid component was rendered all the more difficult by reason of the special physical and chemical properties of the polysaccharide. In a previous publication (Beavan and Jones, *Chem. and Ind.*, 1939, 58, 363) attention was drawn to the difficulties encountered in methylating pectic acid both by the methyl sulphate and by the thallium methylation technique. This difficulty was in part overcome by methylating a degraded pectic acid derivative prepared by boiling crude pectin with methyl alcoholic hydrogen chloride (Morrel, Bauer, and Link, *J. Biol. Chem.*, 1935, 105, 1; Hirst, Jones, and Jones, *J.*, 1939, 1880). This procedure destroyed the more labile araban and galactan and converted the pectic acid into the methyl ester of a degraded polygalacturonide of approximately eighteen residues. The physical properties of this material, designated "polyester" by Morrel, Bauer, and Link, made it more amenable to methylation by the thallium technique (Menzies, *J.*, 1926, 937; Hirst and Jones, *J.*, 1938, 497) and by this method the methylated derivatives of strawberry and apple polyesters were prepared and examined. The present results indicate that these polyesters are similar in constitution to the methylated polygalacturonic acids which have been previously examined (Smith, *Chem. and Ind.*, 1939, 58, 363; Beavan and Jones, *loc. cit.*; Luckett and Smith, *J.*, 1940, 1106).



Proof of the constitution of the methylated polyester was furnished by the following observations: the methylated polyuronide gave, on hydrolysis with methyl alcoholic hydrogen

chloride under pressure, 2:3-dimethyl methyl-*d*-galacturonoside methyl ester (I) as a mixture of its pyranose and furanose forms (cf. Lockett and Smith, *loc. cit.*). On hydrolysis with aqueous acid (I) was converted into 2:3-dimethyl *d*-galacturonic acid (II) identified after oxidation and esterification as the crystalline γ -lactone methyl ester (IIIa) of 2:3-dimethyl *d*-mucic acid (IIIb). The constitution of this crystalline product followed from its reaction with periodic acid, which gave the half-aldehyde of *l*(+)-dimethoxysuccinic acid (IV), identified as *l*(+)-dimethoxysuccinamide (V), and glyoxylic acid (VI), identified by its colour reaction with casein and sulphuric acid.

The polyester from both strawberry and apple pectin must therefore be a polymer built up of *d*-galacturonic acid residues in which the hydroxyl groups on C₂ and C₃ are free. The two structures which are in agreement with this evidence are (VII) and (VIII), of which the pyranose form (VIII) is by far the more probable since the pyranose structure alone would display the resistance to acidic hydrolysis so characteristic of the pectic acid molecule. That the linkage



between the galacturonic acid residues is of the α -type is shown by the high positive rotation of pectic acid. It is clear, therefore, that a polygalacturonide with this structure cannot be transformed directly by decarboxylation at C₆ into an araban of the type found associated with pectic acid, since this araban is known to possess a branched chain structure of *l*- α -arabofuranose residues (IX) linked to each other in three different ways—namely, through C₁ (A1...), through C₁ and C₆ (...5A1...), and through C₁C₃ and C₅ (...⁵A1...). Nor can the pectic acid arise from the galactan (X) by oxidation of the primary alcohol groups, since the sugar residues in (X) are linked by β -links. It follows, therefore, that if galactan (X) is the source of araban, then hydrolysis followed by re-synthesis of the oxidised and decarboxylated sugar must intervene.

EXPERIMENTAL.

Strawberry Pectic Acid.—The pectin was obtained from strawberry juice, for a supply of which we wish to express our thanks to Dr. V. L. S. Charley and Carter and Co. of Bristol. The crude pectin was contaminated with kieselguhr; it was triturated with 90% alcohol and filtered to remove colouring matter. The solid was dried at 40°/12 mm. and extracted with the calculated quantity of dilute sodium hydroxide solution. The sludge was spun on the centrifuge and the top clear, light blue solution poured with stirring into 5 vols. of 90% alcohol acidified with hydrochloric acid. Pectic acid was precipitated; it was filtered off, washed with alcohol until free from hydrochloric acid, and dried under reduced pressure; $[\alpha]_D^{20} + 251^\circ$ (in neutral aqueous solution) [Found: Uronic anhydride, 84.0 (calc. from the yield of carbon dioxide evolved on boiling with 12% hydrochloric acid); pentosan, 4.1 (calc. from the yields of furfuraldehyde and carbon dioxide evolved on boiling with 12% hydrochloric acid); galactan, 9.9 (by difference); OMe, 0.2%; equiv., 225].

Strawberry Pectin Polyester (see Morrel, Bauer, and Link, *loc. cit.*).—Strawberry pectic acid (100 g.) was refluxed with stirring with 3% methyl alcoholic hydrogen chloride (1 l.). After 24 hours sufficient concentrated methyl alcoholic hydrogen chloride was added to bring the concentration up to 5% and the refluxing continued for a further 66 hours. The cooled reaction mixture was spun on the centrifuge and the dark slimy solid thus obtained washed with methyl alcohol until free from hydrogen chloride. The solid was dried at 60°/12 mm. and then extracted thrice with boiling water (500 c.c.). The extracts were spun on the centrifuge and the clear solution was poured into alcohol (2½ l.). The precipitated polyester (65 g.) was separated on the centrifuge, washed with alcohol and acetone, and dried at 50°/12 mm.; $[\alpha]_D^{20} + 234^\circ$ (c, 1.2) (Found: OMe, 17.4%; equiv., 200).

A sample of the polyester was titrated with the calculated quantity of barium hydroxide and the resulting barium salt precipitated with alcohol. The white solid was filtered off, washed with alcohol,

and dried in a vacuum (Found: Ba, 25.1; OMe, 1.8. A methylpolygalacturonoside methyl ester containing eight units requires Ba, 27.7; OMe, 1.6%).

Methylation of Strawberry Polyester.—The polyester (5.7 g.) was dissolved in water (20 c.c.) and to it was added a hot concentrated solution of thallium hydroxide (30 c.c. of 6*N*). The cream-coloured precipitate was filtered off, washed with methyl alcohol and ether, and dried at 40°/12 mm. The orange solid was ground to a powder (120 mesh) and boiled with methyl iodide for 72 hours under reflux with the exclusion of light and moisture. Excess of methyl iodide was distilled off and the residue extracted exhaustively with methyl alcohol. The extracts on concentration gave partially methylated strawberry polyester as a pale brown solid (4.6 g.). The partially methylated material was dissolved in alcohol and evaporated to dryness with the addition of a benzene solution of thallous ethoxide (5 equivs.). The resulting brown solid was powdered (120 mesh) and boiled with methyl iodide until the thallium iodide was neutral to litmus. Methylated strawberry polyester was isolated, as described above, as a stiff brown syrup (4.35 g.) (Found: OMe, 42.4%). The syrup was separated into two fractions by precipitation from a chloroform solution with ether. (A) Ether-insoluble (2.15 g.); $[\alpha]_D^{20} + 144^\circ$ (c, 0.66 in methyl alcohol) (Found: OMe, 39.9%). A dimethyl uronic methyl ester polymer requires OMe, 42.7%. (B) A stiff brown syrup obtained on evaporation of the ethereal extract (2.20 g.), which was not further examined.

Hydrolysis. The methylated polyester was extremely resistant to hydrolysis, but this could be effected by the use of methyl alcoholic hydrogen chloride under pressure. The material (2.10 g.) was dissolved in 3% methyl alcoholic hydrogen chloride (35 c.c.) and heated at 140° in a sealed tube for 24 hours. The hydrolysis mixture was nearly neutral and a considerable pressure developed in the tube owing to the formation of methyl chloride and carbon dioxide. The solution was neutralised with silver carbonate, filtered, and evaporated under diminished pressure to a dark brown syrup (1.85 g.). This was separated into two fractions by extraction with ether—(1) an ether insoluble solid which consisted of incompletely hydrolysed material, and (2) an ether-soluble syrup consisting of the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside [1.5 g., $n_D^{18} 1.473$, $[\alpha]_D^{20} - 27^\circ$ (in acetone)]. This was fractionally distilled in a vacuum giving: (a) the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside (0.90 g.), b. p. 150°/0.001 mm. (bath temp.), $n_D^{18} 1.4618$, $[\alpha]_D^{21} - 38^\circ$ (c, 3.0 in water) (Found: OMe, 48.2; equiv., 254. Calc. for $C_{10}H_{14}O_7$: OMe, 49.6%; equiv., 250); (b) a fraction, b. p. 180°/0.01 (0.3 g.), $n_D^{18} 1.4738$, which was partly crystalline, the crystals which separated after tiling having m. p. 211° not raised on recrystallisation from ether; (c) still residue (0.3 g.).

The distilled ester (0.87 g.) was hydrolysed with *N*-hydrochloric acid (30 c.c.) at 90–95°: $[\alpha]_D^{21} - 38^\circ$ (initial value); + 31° (25 minutes); + 52° (1 hour); + 59° (1½ hours, constant value). The solution was neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. Removal of the solvent at 40°/12 mm. left 2:3-dimethyl *d*-galacturonic acid (0.8 g.), $[\alpha]_D^{20} + 63^\circ$ (c 1.11 in water) (Found: OMe, 25.9; equiv., 212. Calc. for $C_8H_{14}O_7$: OMe, 27.9%; equiv., 222), which was oxidised with bromine water; the resultant 2:3-dimethyl *d*-mucic acid (0.8 g.) was isolated as a syrup, $[\alpha]_D^{21} - 20^\circ$ (c, 0.99 in methyl alcohol) (Found: OMe, 25.0; equiv., 122. Calc. for $C_8H_{14}O_8$: OMe, 26.9%; equiv., 119). The acid (0.70 g.) was esterified by boiling with 2% methyl alcoholic hydrogen chloride for 15 hours. The cooled solution was neutralised with silver carbonate, filtered, and evaporated to a syrup, which was extracted with ether. The solvent was distilled off, leaving the syrupy ester (0.72 g.), $n_D^{18} 1.4688$, $[\alpha]_D^{20} - 5^\circ$ (c, 0.78 in methyl alcohol) (Found: OMe, 38.8%), a portion of which (0.40 g.) was distilled under reduced pressure giving the methyl ester of the 1:4-lactone of 2:3-dimethyl *d*-mucic acid (0.33 g.), b. p. 160°/0.001 mm. (bath temp.), $n_D^{18} 1.4658$, $[\alpha]_D^{20} - 40^\circ$ (in water) (Found: equiv., 118). This crystallised on standing and was recrystallised from ether. It had m. p. 77–78°, raised to 96° on drying in a vacuum (Found, on a dried sample: C, 46.2; H, 5.8; OMe, 38.4. Calc. for $C_8H_{14}O_7$: C, 46.2; H, 6.0; OMe, 39.7%).

The ester lactone (0.26 g.), m. p. 96°, was oxidised with the calculated quantity of periodic acid in water (10 c.c.): $[\alpha]_D^{22} - 40^\circ$ (initial value); - 10° (5 minutes); + 12° (12 hours, constant value). The solution was neutralised with barium carbonate, filtered, and concentrated to about 5 c.c. A small portion of the solution at this stage gave with casein and sulphuric acid a strong positive test for glyoxylic acid. Barium carbonate (1 g.) and bromine (1 c.c.) were added to the solution which became non-reducing towards Fehling's solution after 12 hours. The solution was aerated to remove excess of bromine and filtered. The filtrate was evaporated to dryness and the residue esterified by boiling with 2% methyl alcoholic hydrogen chloride (90 c.c.). The cooled solution was neutralised with silver carbonate and filtered, and the solvent evaporated at 60°/12 mm. The solid residue was exhaustively extracted with ether and the extracts were concentrated in a vacuum to a syrup (0.20 g., $n_D^{20} 1.4348$) which was distilled giving the dimethyl ester of *l*(+)-dimethoxysuccinic acid (0.15 g.), b. p. 90–110°/0.001 mm. (bath temp.), $n_D^{21} 1.4322$, $[\alpha]_D^{20} + 77^\circ$ (c, 2.46 in methyl alcohol) (Found: OMe, 58.2. Calc. for $C_8H_{14}O_8$: OMe, 60.2%). The ester (120 mg.) with methyl alcoholic ammonia gave needle-shaped crystals of the diamide of *l*(+)-dimethoxysuccinic acid (75 mg.), m. p. and mixed m. p. 280° (decomp.), $[\alpha]_D^{20} + 96^\circ$ (c, 0.73 in water).

Apple Pectin Polyester.—Apple pectic acid (Hirst and Jones, *J.*, 1939, 456) (uronic anhydride, 73.0; OMe, 10.2%; equiv., 250; $[\alpha]_D^{28} + 230^\circ$) was converted by boiling with methyl alcoholic hydrogen chloride in the usual manner into the polyester which was isolated, as described above, as a snow-white powder. Yield, 65%; $[\alpha]_D^{29} + 226^\circ$ (in neutral aqueous solution) (Found: OMe, 17.4%; equiv., 195). A sample of the polyester was treated with the calculated quantity of barium hydroxide and the resulting barium salts were precipitated by alcohol. The white solid was filtered off, washed with alcohol, and dried in a vacuum (Found: Ba, 24.6; OMe, 1.5. A methylpolygalacturonoside methyl ester containing eight units requires Ba, 27.7; OMe, 1.6%).

Methylation. The polyester (6.0 g.) was dissolved in water (30 c.c.) and a hot solution of 2*N*-thallous hydroxide (100 c.c.) was added. The precipitated white thallium derivative was filtered off, washed with alcohol and ether, and dried at 60°/12 mm. The powdered solid (120 mesh) was boiled with methyl iodide under reflux with the exclusion of light and moisture until the solid no longer had an alkaline

reaction. The solution was worked up as described for the strawberry polyester. Two further methylations with thalious ethoxide solution gave methylated apple polyester as a syrup (5.4 g.). This was dissolved in chloroform and separated by the addition of ether into (a) a crisp brown solid {1.8 g., $[\alpha]_D^{20} + 146^\circ$ (in methyl alcohol); OMe, 39.9%}, and (b) a syrup which was not further examined.

Hydrolysis. Methylated apple polyester (1.10 g.) was dissolved in 4% methyl alcoholic hydrogen chloride (25 c.c.) and heated under pressure at $140-150^\circ$ for 24 hours. The cooled solution was neutralised with silver carbonate, filtered, and evaporated to a syrup (0.95 g.) which was exhaustively extracted with ether. Evaporation of the ether left a syrup (0.80 g.), $n_D^{21} 1.4842$, $[\alpha]_D^{20} - 15^\circ$ (c, 1.0 in acetone), which was distilled in a vacuum giving: (1) 0.10 g., b. p. up to $130^\circ/0.001$ mm. (bath temp.), $n_D^{21} 1.4805$; (2) the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside (0.39 g.), b. p. $160^\circ/0.001$ mm. (bath temp.), $n_D^{19} 1.4645$, $[\alpha]_D^{30} - 30^\circ$ (c, 1.5 in water) (Found: OMe, 48.1%); (3) 0.1 g. of syrup which partly crystallised, b. p. $175-200^\circ/0.001$ mm.

Fraction (2) (0.37 g.) was hydrolysed with *N*-hydrochloric acid (25 c.c.): $[\alpha]_D^{20} - 30^\circ$ (initial value); $+ 47^\circ$ ($1\frac{1}{2}$ hours); $+ 51^\circ$ (3.75 hours, constant value). The cooled solution was neutralised with silver carbonate, and filtered before and after the passage of hydrogen sulphide. Evaporation of the solvent gave 2:3-dimethyl *d*-galacturonic acid (0.32 g.), $[\alpha]_D^{20} + 35^\circ$ rising to $+ 58^\circ$ in 1 hour (c, 6.0 in water) (Found: OMe, 26.9; equiv., 226. Calc. for $C_6H_{10}O_7$: OMe, 27.9%; equiv., 222). The acid (0.30 g.) was dissolved in water (7 c.c.) and oxidised with bromine (1 c.c.) for 12 hours. The solution was then non-reducing. Bromine was removed by aeration and the solution neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. Evaporation of the solution gave 2:3-dimethyl *d*-mucic acid (0.30 g.) which was converted into the methyl ester of the 1:4-lactone of 2:3-dimethyl *d*-mucic acid by boiling 3% methyl alcoholic hydrogen chloride (50 c.c., 7 hours). The solution was worked up in the usual manner and the crude ester lactone (0.31 g.) distilled giving the methyl ester of the 1:4-lactone of 2:3-dimethyl *d*-mucic acid (0.26 g.), b. p. $160^\circ/0.001$ mm. (bath temp.), $n_D^{20} 1.4650$. The distillate crystallised on nucleation with an authentic specimen of the ester lactone. Trituration with ether and filtration gave crystals (0.20 g.), m. p. and mixed m. p. with an authentic specimen, 96° (Found: OMe, 38.6%).

The authors thank the Colston Research Society, Bristol, and Imperial Chemical Industries for grants.

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[Received, December 6th, 1946.]

229. Pectic Substances. Part VI. The Structure of the Araban from *Arachis Hypogaea*.

By E. L. HIRST and J. K. N. JONES.

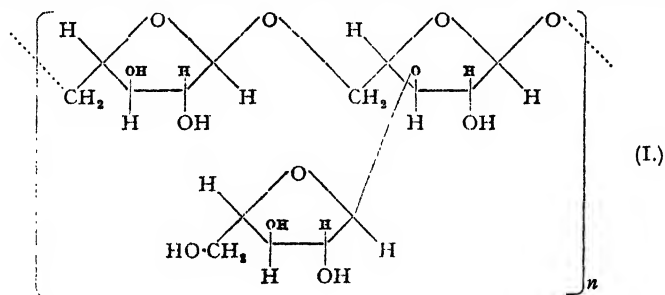
The constitution of the araban component of the pectic material present in the peanut (*Arachis Hypogaea*) has been further investigated. On hydrolysis of the methylated araban, trimethyl methyl-*l*-arabofuranoside, 2:3-dimethyl methyl-*l*-arabinoside, and a monomethyl methyl-*l*-arabinoside were isolated in the approximate proportions 1:1:1. The monomethyl arabinose has now been identified as the 2-methyl derivative, and no other monomethyl *l*-arabinose could be detected. The bearing of these results on the structure of araban is discussed.

ARABANS isolated from several sources of pectin have already been examined, and in all cases it has been demonstrated that on hydrolysis the methylated polysaccharide gave rise to three derivatives of arabinose in approximately equal proportions (Hirst and Jones, *J.*, 1938, 496; 1939, 454, 456, 1865). These arabinose derivatives were identified as 2:3:5-trimethyl *l*-arabofuranose, 2:3-dimethyl *l*-arabinose, and a monomethyl *l*-arabinose which was provisionally identified as 3-methyl *l*-arabinose. The identification of this substance was dependent upon the following observations: (1) The sugar had no methoxyl group on C_5 , since on acidic hydrolysis of the glycoside it gave a derivative of *l*-arabopyranose characterised by its high positive rotation; (2) it had a hydroxyl group on C_4 , since on oxidation it gave a furano-lactone showing a negative rotation and a characteristic slow rate of hydrolysis. Moreover, the rate of hydrolysis of the original araban indicated that all the arabinose components were present in the furanose form and therefore that the hydroxyl group on C_4 was engaged in ring formation and could not be replaced by a methoxyl group after methylation (Hirst and Jones, *J.*, 1939, 454). Only two possibilities, therefore, for the monomethyl derivative remained. It could be either 2- or 3-methyl *l*-arabinose. The latter was thought to be the sugar present in the hydrolysis products of the methylated araban since the amide from the syrupy hydrolysis product gave a positive Weerman test, indicating the presence of an α -hydroxy-amide. It has now been ascertained that this positive test was due to the presence of a small quantity of *l*-arabonamide in the crude syrupy amide, a trace of *l*-arabinose being present in the monomethyl arabinose fraction owing to the difficulty encountered in separating

these two high boiling fractions. In order to obtain further insight into the constitution of the monomethyl arabinose the two sugars, 2- and 3-methyl *l*-arabinose were synthesised and crystalline derivatives of them were prepared (Jones, Kent, and Stacey, in the press; Hirst, Jones, and Williams, in the press). Crystalline derivatives have now been obtained from the monomethyl fraction of the hydrolysis products from methylated araban, and by comparison of these with the synthetic material it has been established beyond doubt that the monomethyl fraction consists almost exclusively of 2-methyl *l*-arabinose (see experimental section). The isolation of the crystalline 2-methyl *l*-arabinose phenylhydrazone, 2-methyl 3:4-monoacetone *l*-arabinose, and 2-methyl *l*-arabonamide derivatives from the monomethyl fraction was aided by the previous preparation of synthetic crystalline derivatives and by the fact that larger quantities of methylated araban of higher purity were available. This was rendered possible by the observation that araban, which was the major component of the pectin, was methylated much more rapidly than galactan and pectic acid and that the latter can be converted into soluble acid products on heating with 30% sodium hydroxide in the presence of air without destruction of the araban.

With the larger quantities of methylated araban available, it was possible to carry out a rigorous fractionation of the methylated product and thus to obtain a homogeneous product which showed $[\alpha]_D^{20} - 180^\circ$ in methyl alcohol. It was demonstrated, from observation of the refractive indices and methoxyl values of the fractions obtained on distillation of the products of methanolysis of the methylated araban, that trimethyl, dimethyl, and monomethyl arabinoses are present in equimolecular proportions. The trace of unmethylated arabinose which is also present appears to arise either through incomplete methylation of the polysaccharide or by demethylation of the arabinose fractions during methanolysis.

From these observations the general type of structure present in the araban becomes apparent. The polysaccharide contains only the three residues $41 \dots, \dots 541 \dots$, and $\dots 341 \dots$ present in equimolecular proportions, *A* representing an arabofuranose unit linked through the positions indicated. A branched chain structure with terminal arabofuranose residues is clearly present, but the present data do not enable us to differentiate between a main chain of arabofuranose residues composed solely of $\dots 341 \dots$ residues and one comprising both this residue and $\dots 541 \dots$. From rotational data the *l*-arabofuranoside links have the α -configuration, and the general lines of the structure are illustrated in (I) which represents one



of the formulæ consonant with the experimental observations, but it is obvious that certain simple variations of this formula are also in agreement with the available experimental evidence. The problem of distinguishing between these requires the development of novel methods of attack, and experimental work is now being undertaken with this object in view. The branched chain of this polymer, which is composed only of *l*-arabofuranose residues, proves that the araban cannot be formed in the plant directly, as a polymer, by simple processes of oxidation and decarboxylation from either the galactan or the pectic acid associated with pectin. The origin and mechanism of the formation of araban remains therefore to be determined.

EXPERIMENTAL.

The seeds (14 kg.) were defatted with benzene and the protein was removed in the usual manner. The residual material was extracted with aqueous potassium hydroxide and crude araban isolated using the conditions described by Hirst and Jones (*loc. cit.*). A portion (50 g.) of the isolated polysaccharides (100 g.) was methylated with sodium hydroxide and methyl sulphate. After two methylations crude methylated araban was isolated by the addition of acetone followed by filtration of the solution to remove insoluble sodium salts and polysaccharide material. After the insoluble methylated material had been separated the aqueous solution was acidified and extracted with chloroform. Concentration of the extract gave some methylated pectic acid (4 g.), $[\alpha]_D^{25} + 114^\circ$ (*c*, 0.57 in methyl alcohol) (Found: OMe,

38%). The filtered acetone solution on evaporation gave a pale yellow sticky solid which was further methylated by use of Purdie's reagents. The polysaccharide (35 g.) was fractionated from chloroform (100 c.c.) by the gradual addition of light petroleum (b. p. 40–60°), giving:

Fraction A (0.9 g.), mainly inorganic material.

Fraction B (6.2 g.), $[\alpha]_D^{25} = 144^\circ$ (c, 1.1 in methyl alcohol) (Found: OMe, 38.7%).

Fraction C (15 g.), $[\alpha]_D^{25} = 176^\circ$ (c, 1.3 in methyl alcohol) (Found: OMe, 38.3%).

Fraction D (8.1 g.), $[\alpha]_D^{25} = 180^\circ$ (c, 0.7 in methyl alcohol) (Found: OMe, 38.0%).

Fraction E (4.0 g.), $[\alpha]_D^{25} = 179^\circ$ (c, 0.9 in methyl alcohol) (Found: OMe, 38.0%).

All these fractions were pale yellow sticky solids. The residue (1.0 g.) was discarded.

Trial Hydrolysis.—Fraction D (7.9 g.) was dissolved in methyl alcohol (75 c.c.)–water (25 c.c.) containing oxalic acid dihydrate (0.1 g.) and boiled under reflux in an attempt to bring about a graded hydrolysis of the polysaccharide (see Hirst and Young, *J.*, 1939, 1480). The optical rotation (-184°) remained constant and no hydrolysis occurred during 20 hours under these conditions even when the oxalic acid concentration was raised to 0.5 g./100 c.c. Accordingly, oxalic acid was removed by neutralisation with calcium carbonate and the unchanged polysaccharide submitted to hydrolysis with boiling methyl alcohol (100 c.c.) containing hydrogen chloride (2 g.) for 30 hours. Change of optical rotation could not be observed owing to darkening of the solution. The cooled solution was neutralised by cautious addition of ethereal diazomethane and the solvents were removed at 60°. The residual syrup (9.4 g.) was then fractionated by continuous extraction from aqueous solution (Z) with light petroleum (b. p. 40–60°) giving an extract—*Fraction 1* (2.89 g.), $n_D^{20} 1.4360$ —which was distilled yielding *Fraction 1a* (2.54 g.), b. p. 130°/12 mm., $n_D^{20} 1.4352$ (Found: OMe, 60.0%), and a still residue (0.28 g.). The aqueous solution (Z, above) was then extracted continuously with ether and the extracts concentrated at 40° to a syrup—*Fraction 2* (3.68 g.)—which was added to the still residue (0.28 g. above) and the whole fractionally distilled giving *Fraction 2a* (1.3 g.), b. p. 120°/0.2 mm., $n_D^{20} 1.4452$ (Found: OMe, 52.3%); *Fraction 2b* (1.87 g.), b. p. 125°/0.01 mm., $n_D^{20} 1.4487$ (Found: OMe, 47.8. Calc. for $C_8H_{14}O_5$: OMe, 48.4%); still residue (S, 0.62 g.). The aqueous solution (Z) after extraction with light petroleum and ether was evaporated in a vacuum to a syrup which was combined with the still residue (S, 0.62 g.) and the mixture (2.8 g.) distilled under reduced pressure giving *Fraction 3a* (0.25 g.), b. p. 125°/0.01 mm., $n_D^{20} 1.4582$ (Found: OMe, 43.7%); *Fraction 3b* (1.06 g.), b. p. 125°/0.01 mm., $n_D^{20} 1.4662$ (Found: OMe, 42.2%); *Fraction 3c* (0.68 g.), b. p. 125°/0.01 mm., $n_D^{20} 1.4750$ (Found: OMe, 24.8%), and a still residue (0.76 g.) (Found: OMe, 25.1%).

Fraction 1a on hydrolysis gave 2:3:5-trimethyl *l*-arabofuranose in quantitative yield, $[\alpha]_D^{20} = 38^\circ$ (in water), identified by conversion into the crystalline lactone, m. p. 29°, of 2:3:5-trimethyl *l*-arabonolactone and into 2:3:5-trimethyl *l*-arabonamide, m. p. 139°. Fraction 2a was a mixture of the methyl glycosides of 2:3:5-trimethyl *l*-arabofuranose and 2:3-dimethyl *l*-arabinose since it was separated into 2:3:5-trimethyl methyl-*l*-arabinoside (0.90 g.), identified as crystalline 2:3:5-trimethyl *l*-arabonolactone, m. p. 29°—prepared in the usual manner—and 2:3-dimethyl methyl-*l*-arabinoside (0.35 g.), $n_D^{20} 1.4454$, on fractional extraction from aqueous solution with light petroleum (b. p. 40–60°). This last fraction was combined with Fraction 2b and the whole (2.1 g.) hydrolysed with *N*-hydrochloric acid at 100°; $[\alpha]_D^{20} = 35^\circ \rightarrow [\alpha]_D^{20} = 92^\circ$ (constant value). The resultant syrup (1.9 g.) ($[\alpha]_D^{18} + 104^\circ$, c, 1.1 in water) (Found: OMe, 34.4. Calc. for $C_7H_{14}O_5$: OMe, 34.6%), isolated in the usual manner, was mainly if not entirely 2:3-dimethyl *l*-arabinose since it gave, in good yield, the corresponding 2:3-dimethyl anilino-*l*-arabinose, m. p. and mixed m. p. 139°. On refluxing it with alcoholic aniline, no other derivative of arabinose could be detected.

Fractions 3a and 3b were combined (1.80 g.) and separated by fractional extraction from water with ether into 2:3-dimethyl methyl-*l*-arabinoside (0.8 g.), identified, after hydrolysis to 2:3-dimethyl *l*-arabinose with *N*-hydrochloric acid, as 2:3-dimethyl anilino-*l*-arabinose, m. p. and mixed m. p. 139°. The more water-soluble fraction (1.0 g.) was 2-monomethyl methyl-*l*-arabinoside which was combined with Fraction 3c and the whole (1.65 g.) hydrolysed with boiling *N*-sulphuric acid (25 c.c.); $[\alpha]_D^{20} + 81^\circ$ (constant value) $\rightarrow +94^\circ$ (constant value after 6 hours). The residual syrup (1.3 g.) did not crystallise (Found: OMe, 19.4. Calc. for $C_6H_{12}O_5$: OMe, 18.9%). A sample, on refluxing with alcoholic phenylhydrazine, gave 2-methyl *l*-arabinose phenylhydrazone, m. p. and mixed m. p. 115° (see below). On shaking a sample of the syrup with acetone and anhydrous copper sulphate, 2-methyl monoacetone *l*-arabinose was formed in quantitative yield, m. p. and mixed m. p. 117° (Found: C, 52.7; H, 7.8; OMe, 15.2. Calc. for $C_9H_{16}O_5$: C, 52.9; H, 7.8; OMe, 15.2%).

A portion (0.66 g.) of the still residue was hydrolysed with hot *N*-sulphuric acid (18 c.c.). The syrup (0.56 g.), $[\alpha]_D + 92^\circ$ (Found: OMe, 17.4%), isolated in the usual manner was almost entirely 2-methyl *l*-arabinose since it gave the corresponding crystalline phenylhydrazone, m. p. and mixed m. p. 115°, on refluxing with an alcoholic solution of phenylhydrazine. Some *l*-arabinose was also present since the syrup gave, in small yield with an alcoholic solution of benzoylhydrazine, a precipitate of *l*-arabinose benzoylhydrazone, m. p. 184°.

Large Scale Hydrolysis of Methylated Arabin.—Fraction C (14.46 g.) was hydrolysed by boiling with methanolic hydrogen chloride (100 c.c.; 1%) for 12 hours. Changes in optical rotation were not observable owing to darkening of the solution. The cooled solution was neutralised with a slight excess of diazomethane in ether and the solvents were removed as quickly as possible at 70°. The syrupy residue (17.1 g.) was then dissolved in water (50 c.c.) and extracted continuously for 24 hours in an all-glass apparatus with light petroleum (sulphur-free, b. p. 35–37°). After removal of the solvent at 40° there remained a syrup (7.05 g., $n_D^{20} 1.4388$). The aqueous solution was then extracted continuously for a further 24 hours with ether. Concentration of the extracts gave a syrup (4.75 g.). The residual aqueous solution on removal of water gave a syrup (5.2 g.) which was extracted with chloroform, giving a syrup (5.0 g.) soluble in chloroform and leaving crystalline β -methyl-*l*-arabopyranoside (0.2 g.), m. p. 164–168° not depressed on admixture with an authentic specimen.

Fractional Distillation of the Syrups.—The light-petroleum-soluble syrup (7.05 g., $n_D^{20} 1.4388$) was

distilled at 20 mm., giving: *Fraction 4* (4.94 g.), b. p. 145° (bath temp.), n_D^{20} 1.4359 (Found: OMe, 59.2. Calc. for $C_9H_{18}O_5$: OMe, 60.2%); *Fraction 5* (1.46 g.), b. p. 155°, n_D^{20} 1.4432 (Found: OMe, 54.0. Calc. for $C_9H_{18}O_5$: OMe, 48.4%). The still residue (0.69 g.) was added to the ethereal extract (4.75 g.) and the whole distilled at 0.01 mm. giving *Fraction 6* (2.34 g.), b. p. 110° (bath temp.), n_D^{20} 1.4515 (Found: OMe, 48.4. Calc. for $C_8H_{16}O_5$: OMe, 48.4%). The syrup soluble in chloroform (5 g., see above) was added at this stage and the distillation continued. *Fraction 7* (2.55 g.), b. p. 140° (bath temp.), n_D^{20} 1.4565 (Found: OMe, 48.1. Calc. for $C_8H_{16}O_5$: OMe, 48.4%); *Fraction 8* (2.11 g.), b. p. 155° (bath temp.), n_D^{20} 1.4672 (Found: OMe, 40.3. Calc. for $C_7H_{14}O_5$: OMe, 34.8%); *Fraction 9* (1.06 g.), b. p. 160° (bath temp.), n_D^{20} 1.4715 (Found: OMe, 34.9. Calc. for $C_7H_{14}O_5$: OMe, 34.8%); *Fraction 10* (0.65 g.), b. p. 190° (bath temp.), n_D^{20} 1.4745 (Found: OMe, 32.1. Calc. for $C_7H_{14}O_5$: OMe, 34.8%). The still residue (1.20 g.) (Found: OMe, 30.5%) was methylated with Purdie's reagents (see below).

Examination of the Fractions.—A portion of *Fraction 4* (4.84 g.) was dissolved in *N*-sulphuric acid (25 c.c.) and hydrolysed at 90° for 3½ hours; $[\alpha]_D^{20} - 86^\circ \longrightarrow -30^\circ$ (constant value). The sugar (4.5 g.) was isolated by continuous extraction of the solution with chloroform (Found: OMe, 48.0. Calc. for $C_8H_{16}O_5$: OMe, 48.4%). The sugar was converted into 2:3:5-trimethyl *l*-arabonolactone by the following general method. The sugar (4.5 g.) was dissolved in *N*-sodium hydroxide (150 c.c.), and iodine (12 g.) added. After 12 hours, excess of iodine was removed with sulphur dioxide and the solution then acidified with sulphuric acid and extracted continuously with chloroform. Concentration of the chloroform extract gave a syrup (4.3 g.), n_D^{20} 1.4448, which crystallised on nucleation with 2:3:5-trimethyl *l*-arabonolactone, m. p. and mixed m. p. with an authentic specimen, 28°. This fraction therefore consists entirely of 2:3:5-trimethyl methyl-*l*-arabinoside.

Fraction 5 (1.45 g.) was dissolved in *N*-sulphuric acid (25 c.c.) and hydrolysed on the steam-bath; $[\alpha]_D^{20} - 81^\circ \longrightarrow [\alpha]_D^{20} + 30^\circ$ (final value). The free sugars (1.35 g.) isolated in the usual manner (Found: OMe, 41.8%) were oxidised with bromine (2 c.c.) in water (5 c.c.) for 12 hours. The lactones—isolated by chloroform extraction of the solution after removal of excess of bromine—were distilled in a vacuum giving impure 2:3:5-trimethyl *l*-arabonolactone (0.7 g.), m. p. 20°, and impure 2:3-dimethyl *l*-arabofuranolactone, b. p. 130° (bath temp.)/0.4 mm., n_D^{20} 1.4578. The lactones gave, with alcoholic ammonia, the corresponding crystalline amides, *viz.*, 2:3:5-trimethyl *l*-arabonamide, m. p. 138°, and 2:3-dimethyl *l*-arabonamide, m. p. 161°. It is inferred that this fraction consists of 2:3:5-trimethyl and 2:3-dimethyl methyl-*l*-arabinoside in approximately equal proportion.

Fraction 6 (2.22 g.) was hydrolysed by boiling with *N*-sulphuric acid (20 c.c.) for 3 hours; $[\alpha]_D^{20} - 51^\circ \longrightarrow +101^\circ$ (constant value). The resultant 2:3-dimethyl *l*-arabinose (2.0 g.) was isolated by exhaustive chloroform extraction of the solution after neutralisation with *N*-sodium hydroxide. Since this fraction showed an inversion of sign the material was 2:3-dimethyl methyl-*l*-arabinoside mainly in the furanose form.

Fraction 7 (2.42 g.) was dissolved in *N*-sulphuric acid and hydrolysed by heating the solution to 90°; $[\alpha]_D^{20} + 56^\circ \longrightarrow +102^\circ$ (constant value). The syrupy sugar was isolated from the neutralised solution by exhaustive chloroform extraction (yield, 2.2 g.). This fraction was 2:3-dimethyl methyl-*l*-arabinoside mainly in the pyranose form.

The sugars from *Fractions 6* and *7* were combined (4.2 g.), $[\alpha]_D^{20} + 104^\circ$ (c, 1.3 in water) (Found: OMe, 34.6. Calc. for $C_7H_{14}O_5$: OMe, 34.8%), and oxidised by dissolving in water (10 c.c.) containing bromine (5 c.c.). The solution became hot and was left for 12 hours. Bromine was then removed, first by aeration, and then by passage of sulphur dioxide. The solution was then extracted exhaustively with chloroform and the resultant 2:3-dimethyl *l*-arabofuranolactone (4.1 g.) purified by distillation in a vacuum; b. p. 140° (bath temp.)/0.5 mm., n_D^{20} 1.4575. With alcoholic ammonia the lactone gave 2:3-dimethyl *l*-arabonamide, m. p. 162°, in quantitative yield.

Fraction 8 was a mixture of 2:3-dimethyl methyl-*l*-arabinoside and 2-methyl methyl-*l*-arabinoside. Partial separation of the components was achieved by the following method. The glycosides (2.0 g.) were dissolved in acetone (25 c.c.) containing hydrogen chloride (1 g.) (see Hirst and Jones, *J.*, 1939, 456). After 20 hours the solution was poured into an aqueous solution of sodium hydrogen carbonate and the neutral solution extracted with chloroform. The extracts were dried (K_2CO_3), filtered, and concentrated to a syrup (1.74 g.) which was distilled under reduced pressure giving a first fraction, b. p. 106° (bath temp.)/0.5 mm. (0.6 g.), n_D^{20} 1.4500 (Found: OMe, 30.0. Calc. for 2-methyl monoacetone methyl-*l*-arabinoside: OMe, 28.4%), and a second fraction, b. p. 120°/0.5 mm. (0.8 g.), n_D^{20} 1.4610 (Found: OMe, 43.0. Calc. for 2:3-dimethyl methyl-*l*-arabinoside: OMe, 48.4%). The still residue was mainly 2-methyl methyl-*l*-arabinoside (Found: OMe, 36.0. Calc. for $C_7H_{14}O_5$: OMe, 34.8%). The impure 2-methyl monoacetone methyl-*l*-arabinoside (0.5 g.) was hydrolysed with boiling *N*-sulphuric acid, $[\alpha]_D^{20} + 100^\circ$ (final value), and the sugar (0.3 g.) isolated in the usual manner. It was identified, after boiling with alcoholic phenylhydrazine, as 2-methyl *l*-arabinose phenylhydrazone, m. p. and mixed m. p. 115°. This same derivative was isolated after boiling the free sugar, obtained from the hydrolysis of the still residue with hot *N*-sulphuric acid, with alcoholic phenylhydrazine. The second fraction (above) on hydrolysis with boiling *N*-sulphuric acid (20 c.c.) gave 2:3-dimethyl *l*-arabinose which was identified as its anilide, obtained by boiling an alcoholic solution of the sugar with aniline, m. p. 138° not depressed on admixture with an authentic specimen.

Fractions 9 and *10* consisted of 2-methyl methyl-*l*-arabinoside. These fractions were combined and the syrup (1.65 g.) hydrolysed with boiling *N*-sulphuric acid (20 c.c.); $[\alpha]_D^{20} + 104^\circ$ (final value; initial value not observable). The free sugar (1.5 g.) was isolated after neutralisation of the solution with barium carbonate followed by filtration and concentration under reduced pressure (Found: OMe, 18.7. Calc. for $C_6H_{12}O_5$: OMe, 18.9%).

A portion of the syrup (0.1 g.) on heating with alcoholic phenylhydrazine gave 2-methyl *l*-arabinose phenylhydrazone (0.1 g.), m. p. 115° not depressed on admixture with an authentic specimen. The syrup (0.4 g.) was oxidised with bromine (1 c.c.) in water (5 c.c.) at 30° for 12 hours. Bromine was removed by aeration and the 2-methyl *l*-arabonolactone isolated by exhaustive extraction of the solution

with chloroform. The lactone (0.35 g.) did not crystallise, but with an alcoholic solution of ammonia it gave 2-methyl *l*-arabonamide (0.3 g.), $[\alpha]_D + 51^\circ$ (*c*, 1.1 in water), m. p. 130° depressed to 124° on admixture with 3-methyl *l*-arabonamide, m. p. 131° (Found: C, 40.1; H, 7.4; N, 7.8; OMe, 17.2. $C_6H_{13}O_5N$ requires C, 40.2; H, 7.3; N, 7.8; OMe, 17.3%). 2-Methyl *d*-arabonamide has $[\alpha]_D - 53^\circ$ (in water), m. p. 131° (Schmidt and Simon, *J. pr. Chem.*, 1942, **152**, 199).

To prove the absence of any quantity of 3-methyl *l*-arabinose, the following procedure was adopted. The syrupy sugar (1.0 g.) was boiled with 3% methyl-alcoholic hydrogen chloride for 24 hours to ensure a maximum conversion into the pyranoside derivative. The solution was neutralised with silver carbonate and filtered, and the residual non-reducing syrup (0.92 g.), $[\alpha]_D^{20} + 143^\circ$ (*c*, 0.9 in water), was dissolved in water and oxidised with excess of sodium periodate solution (30 c.c.; 0.3M) for 24 hours. The aqueous solution was then extracted, first with ether, which is known to extract monomethyl methyl-*l*-arabinoside very slowly indeed, and then with chloroform. Concentration of the ethereal extract gave a mobile reducing syrup (0.7 g.) from which no identifiable product could be isolated. The chloroform extract on concentration gave a sticky brown solid (0.2 g.), which on hydrolysis with *n*-sulphuric acid was completely decomposed with the formation of resinous products. No 3-methyl *l*-arabinose, which would not have been oxidised with sodium periodate, could be detected, nor could any derivative of 3-methyl *l*-arabinose be isolated. It is concluded that any appreciable quantity of 3-methyl *l*-arabinose is absent from the products of hydrolysis of methylated araban.

The still residue (1.2 g.) was methylated with silver oxide and methyl iodide (twice) and the syrupy sugar distilled in a vacuum giving a mobile syrup (0.9 g.), n_D^{20} 1.4480 (Found: OMe, 59.1%), which on hydrolysis with boiling *n*-sulphuric acid gave 2:3:4-trimethyl *l*-arabinose, n_D^{20} 1.4540, $[\alpha]_D^{20} + 112^\circ$ (*c*, 1.1 in water) (Found: OMe, 46.0%).

On oxidation with bromine water the syrup (0.4 g.) gave the corresponding δ -lactone, isolated as the crystalline amide, m. p. 95° (Found: OMe, 44.2. Calc. for $C_8H_{17}O_5N$: OMe, 44.9%).

From an examination of the various fractions, it may be calculated from the values of refractive index and methoxyl of each fraction that the sugars 2:3:5-trimethyl *l*-arabinose, 2:3-dimethyl *l*-arabinose, and 2-methyl *l*-arabinose are present in a ratio approximating very closely to 1:1:1.

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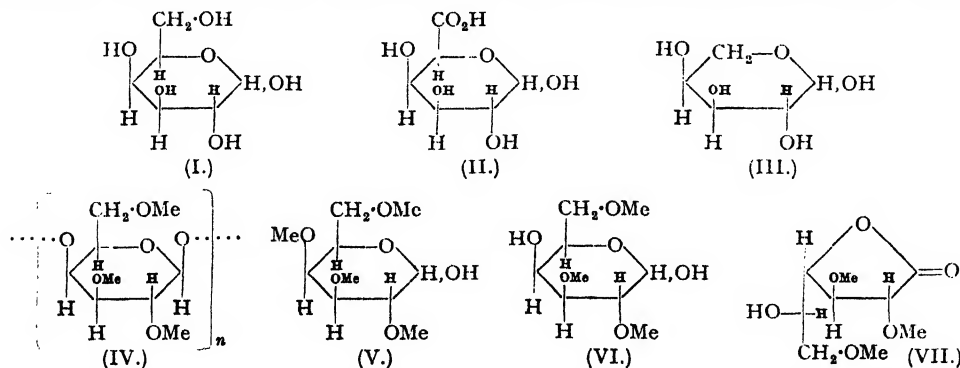
[Received, November 28th, 1946.]

230. Pectic Substances. Part VII. The Constitution of the Galactan from *Lupinus albus*.

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A galactan has been isolated from the pectin component of *Lupinus albus*. This polysaccharide is a linear polymer built up of *d*-galactose residues which, after methylation followed by hydrolysis, yields 2:3:6-trimethyl *d*-galactose together with a small amount of 2:3:4:6-tetramethyl *d*-galactose from the end group. The amount of this latter sugar corresponds to an average repeating unit of approximately 100 galactose residues. The isolation of this polysaccharide is further evidence that galactan is not converted into araban by a simple process of oxidation followed by decarboxylation of the resultant uronic acid residue.

Most samples of pectin on hydrolysis furnish a mixture of the three sugars *d*-galactose (I), *d*-galacturonic acid (II), and *l*-arabinose (III), and at one time it was considered possible that pectin was a single substance which possessed a cyclic structure built up from these residues. Ehrlich, however, demonstrated that pectin contained an araban as a separate entity, and subsequent work has indicated that at any rate most of the arabinose encountered in pectic



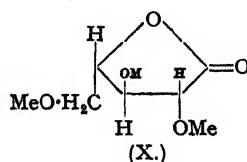
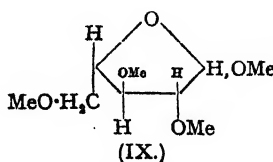
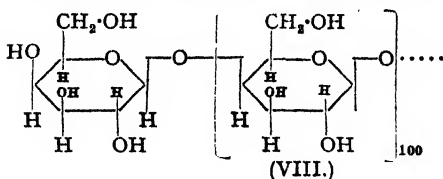
materials is present in the form of this araban component. It seemed probable that the galactose residues also might be present as a separate polysaccharide, and it is shown in the

present communication that the pectic material of the seeds of the white lupin does in fact contain a galactan, which can be separated from the pectic acid and the araban components. Since the conversion of (I) into (III) may proceed in Nature through (II), which then undergoes decarboxylation, it was of considerable interest to examine in detail the constitution of this galactan and to determine whether it was unbranched, as in pectic acid, or branched, as in araban, and thus to decide whether it could be structurally related to either the pectic acid or the araban component of pectin. In the former case the sugar residues should be of the pyranose form and linked through α -linkages, whilst in the latter case the *d*-galactose residues should be of the furanose form.

In common with many other plant materials the seed of the white lupin contains material which on hydrolysis is converted into *d*-galactose and *l*-arabinose ("The Principles of Plant Biochemistry", M. W. Onslow, Cambridge University Press, 1931 Edtn., p. 72). Professor M. Skene of the University of Bristol had informed us that these seeds were a particularly rich source of pectin, and we investigated their carbohydrate content with the object of isolating the galactan component. We found that the carbohydrate fraction of the seed contained a pectin-like material in which the percentage of uronic acid component and of araban was much lower than any other sample of pectin we had hitherto encountered, and thus enabled us to obtain, in a relatively easy manner, a sample of the galactan. Associated with this galactan there was an araban which could be partly removed by extraction with 70% alcohol and a pectic acid which could be precipitated as calcium pectate. The araban showed the same ease of hydrolysis and high negative rotation as the araban associated with apple, citrus, and peanut pectins. The pectic acid component could be converted into a degraded product (see Morrel, Baur, and Link, *J. Biol. Chem.*, 1934, 105, 1) which had properties close to those of the corresponding polysaccharides from apple and citrus pectins.

It was inferred, therefore, that we were dealing with a true pectin which was, however, particularly rich in galactan. This galactan, which could not be obtained completely free from adsorbed araban and pectic acid, had $[\alpha]_D^{20} + 38^\circ$ in water. This value is low since the material still contained some 19% of pentosan and the corrected figure is therefore more likely to be about $+70^\circ$. After methylation with thallium hydroxide and methyl iodide (Menzies, *J.*, 1926, 937; Hirst and Jones, *J.*, 1938, 496) a methylated product was isolated which contained methylated araban and methylated galactan. The small quantity of pectic acid present was very difficult to methylate and was lost during the process (Hirst and Jones, *loc. cit.*). Methylated araban was separated from methylated galactan by extraction of the former from the mixture with ether. The ether-insoluble material had $[\alpha]_D^{20} - 12^\circ$ in methyl alcohol, this negative value being an indication that in methylated galactan the sugar residues are joined together by β -linkages and that the galactan cannot be directly related to pectic acid in which the sugar residues are joined together by α -linkages. Methylated galactan (IV) was resistant to hydrolysis and the rate of reaction corresponded to that of a typical galactopyranoside. Fractional distillation of the sugars formed on methanolysis of the methylated galactan led to the identification of tetramethyl *d*-galactopyranose (V), isolated as its crystalline anilide, and 2:3:6-trimethyl *d*-galactose (VI), identified after oxidation as its crystalline furanolactone (VII). The inferences are, therefore, that the galactan is built up of *d*-galactopyranose residues linked through carbon atoms 1 and 4 and that the molecule is linear. The optical rotatory power of the galactan points to the occurrence of β -galactosido-linkages, and the amount of tetramethyl galactose isolated suggests that there is approximately one end group per 100 galactose residues.

In the absence of evidence concerning molecular weight it is not possible at present to say whether this figure represents the molecular size or the size of the repeating unit in a larger molecule. The type of structure present is shown in (VIII). The methylated araban could



not be obtained in a pure state, and a complete examination of it could not be attempted. Nevertheless, methanolysis of the crude material, which still contained much galactan, gave some 2:3:5-trimethyl methyl-*l*-arabinoside (IX) identified as crystalline 2:3:5-trimethyl

l-arabonolactone (X), the identity of which was confirmed by conversion into the corresponding crystalline amide. These arabofuranose residues were therefore terminal groups of the type previously found to be present in arabans associated with other pectic materials.

It is clear from these results that the araban cannot be formed directly from this galactan by processes of oxidation and decarboxylation at position 6. If phytochemical changes of this type do occur it would be necessary to postulate the participation of three types of galactan and two types of pectic acid in the reactions concerned (cf. Hirst, *J.*, 1942, 70). No evidence for the presence of isomeric pectic acids and galactans in pectic materials has yet been obtained, and it would appear much more likely that the various polysaccharides are formed by separate synthetic reactions. In addition, there remains the problem, still quite unsolved, as to whether the plant can utilise the *d*-galactose residues present in the galactan and convert them after hydrolysis into pectic acid and araban, or whether the synthesis proceeds from material other than *d*-galactose. On the basis of present knowledge the possibility cannot be ruled out that the simultaneous occurrence of the three stereochemically closely related substances *d*-galactose, *d*-galacturonic acid, and *l*-arabinose may have no immediate phytochemical significance.

EXPERIMENTAL.

Extraction of the Polysaccharides from the Seeds of Lupinus albus.—After being soaked overnight in water, the seeds were stripped of their skins and milled twice. The protein matter was then extracted by stirring the finely ground material with aqueous sodium chloride solution (10%) for 3 hours, followed by filtration and repetition of the process thrice. The solid residue was then stirred with aqueous sodium hydroxide (0.2%) thrice for 12 hours at a time. Addition of hydrochloric acid to the filtrate then gave no precipitate, indicating the absence of any appreciable quantities of protein. The solid residue was then boiled with aqueous sodium hydroxide (0.2%) for 3 hours, after which it was filtered and the filtrate poured into methylated spirit (4 vols.). The precipitated polysaccharide was filtered off, washed with alcohol, and dried in a vacuum at 90°. The resulting product was extracted with water, the solution was centrifuged to separate insoluble material, and the polysaccharide was precipitated by addition of methylated spirit acidified with hydrochloric acid. The precipitate was then filtered off, washed until free from acid, and dried in a vacuum at 90°. The product (A) was a non-reducing cream-coloured powder. Yield, 4%. $[\alpha]_D^{20} + 52^\circ$ (as sodium salt in water) [Found: furfuraldehyde, 26.5; uronic anhydride, 8% (corresponding to an equiv. of 2200 and 2% of the total furfuraldehyde); N, nil; OMe, nil; equiv., 1430 (by titration with 0.1N-sodium hydroxide)].

Hydrolysis of the Polysaccharide Material (A).—This material (15 g.) was boiled with N-sulphuric acid (250 c.c.) for 6 hours. Hydrolysis was then complete since the optical rotation and reducing power had become constant. A small quantity of flocculent material (0.8 g.) was removed on the centrifuge and the solution was neutralised with barium carbonate and filtered. The filtrate was concentrated under reduced pressure at 40° and poured into methyl alcohol (50 c.c.), and the precipitated barium salts were removed by filtration. The filtrate from the barium salts was concentrated under reduced pressure to a syrup which crystallised. The crystalline solid, m. p. 157° (3.6 g.), separated by filtration after trituration with methyl alcohol, was *d*-galactose since it gave mucic acid, m. p. 210°, after oxidation with nitric acid, and with methylphenylhydrazine it gave the phenylmethylhydrazone, m. p. and mixed m. p. with an authentic sample 186°.

After removal of crystalline galactose the filtrate was concentrated to a syrup and made up to 250 c.c. with water. An iodometric titration at this stage showed that the solution contained 10.3 g. of sugar calculated as hexose, or 8.6 g. calculated as pentose. Furfuraldehyde determinations on the solution indicated that pentose (3.9 g.) was present. Confirmation of this figure was obtained by determination of arabinose as its diphenylhydrazone by the method of Wise and Peterson (*Ind. Eng. Chem.*, 1930, 22, 362). This determination indicated the presence of arabinose (3.9 g.). Other pentoses, except in traces, were therefore absent. Determination of galactose by the mucic acid method as modified by Wise and Peterson (*loc. cit.*) indicated the presence of galactose (6.1 g.). These figures for arabinose (3.9 g.) and for galactose (6.1 g.) are in agreement with the total sugar content obtained by iodometric titration and show that (A) contains approximately 6% of galactose residues and 26% of arabinose residues. Some pectic acid is also present.

(A) (100 g.) was shaken with 70% methyl alcohol (2½ l.) for 3 months. The slurry was then centrifuged and the supernatant liquid evaporated to dryness. The residual solid (0.1 g.) had $[\alpha]_D^{20} - 119^\circ$ (c. 1.0 in water) and yielded 32% of furfuraldehyde on distillation with 12% hydrochloric acid, corresponding to the presence of 64% of pentose.

Since (A) was possibly a mixture of an araban and galactan, a portion of it (3 g.) was boiled with 0.01N-oxalic acid at 100° until the optical rotation was constant. A small amount of insoluble material which separated appeared to be impure pectic acid; it had $[\alpha]_D^{20} + 157^\circ$ (in water) (Found: equiv., 370). The solution was filtered before and after neutralisation with calcium carbonate, and concentrated to dryness. The residual solid was extracted with methyl alcohol and the solution filtered and concentrated to a syrup (0.285 g.) which had $[\alpha]_D^{20} + 91^\circ$ in water and contained 36% of pentosan (calculated from the yield of furfuraldehyde obtained on distillation with 12% hydrochloric acid). The methyl alcohol-insoluble solid (2.0 g.) gave a negative test for pentoses and had $[\alpha]_D^{20} + 77^\circ$ in water. On hydrolysis with 1% sulphuric acid it gave *d*-galactose, m. p. and mixed m. p. 158°. The phenylmethylhydrazone had m. p. 184°. No other sugar could be detected.

Purification of (A) by removal of calcium pectate. Crude (A) contained some uronic acid (see above) which was largely removed in the following manner. The polysaccharide (80 g.) was dissolved in cold water and neutralised with 0.1N-sodium hydroxide, and calcium chloride solution was added to

precipitate the polyuronide as its calcium salt. The insoluble material was then removed on the centrifuge and the water soluble polysaccharide mixture (B) was precipitated by addition of alcohol (5 vols.); $[\alpha]_D^{20} + 38^\circ$ in water (Found: uronic anhydride, 2%; furfuraldehyde, 9.6%; equiv., 3060).

All attempts to separate completely the pentosan, galactan, and uronic acid fractions of (A) either by acid treatment or by fractional precipitation were unsuccessful. Accordingly, (B) (15 g.) was methylated by the standard thalious hydroxide-methyl iodide procedure (Menzies, *loc. cit.*; Hirst and Jones, *loc. cit.*). The methylation was completed by boiling with methyl iodide and silver oxide. The product (12 g.) (Found: OMe, 42%) was isolated in the usual manner.

Fractionation. The methylated product (12 g.) was dissolved in chloroform (50 c.c.) and fractionated by the portionwise addition of light petroleum (b. p. $40-60^\circ$). By this means the following fractions were obtained: Fraction I (0.9 g.), $[\alpha]_D^{20} - 16^\circ$ in methyl alcohol (Found: OMe, 40.3%). Fraction II (8.1 g.), $[\alpha]_D^{20} - 12^\circ$ in methyl alcohol (Found: furfuraldehyde (on boiling with 12% hydrochloric acid, see Bott and Hirst, *J.*, 1932, 2621), 3.1; OMe, 39.1%). Fraction III (2 g.), $[\alpha]_D^{20} - 12^\circ$ in methyl alcohol (Found: OMe, 39.9%). Fraction IV (0.5 g.), $[\alpha]_D^{20} - 13^\circ$ in methyl alcohol (Found: OMe, 39.2%). Fraction V (0.4 g.), $[\alpha]_D^{20} - 15^\circ$ in methyl alcohol (Found: furfuraldehyde, 9.5; OMe, 37.5%).

Fractions I, II, III, and IV were combined and re-methylated with silver oxide and methyl iodide since their methoxyl content was still low. The product, isolated in the usual manner, was separated into two fractions by extraction with boiling methyl iodide. This separation of the methylated polysaccharide into methyl iodide-soluble and -insoluble fractions indicated that there was a substantial difference in the physical properties of the two components. The analytical figures and optical rotations, however, showed little difference between the two fractions. This was confirmed on examination of the products of methanolysis of the two fractions (see below). The solubility difference observed is due probably to difference in molecular weight and not to a substantial difference in chemical constitution. No pentose could be detected in the products of hydrolysis of either fraction.

The methyl iodide-soluble material (4.0 g.) had $[\alpha]_D^{20} - 15.7^\circ$ in methyl alcohol (Found: C, 51.0; H, 7.7; OMe, 39.5%). No acidic groups (uronic acids) were present. The methyl iodide-insoluble material (7.4 g.) had $[\alpha]_D^{20} - 17^\circ$ in methyl alcohol (Found: C, 51.6; H, 7.9; OMe, 41.6%). No acid groups (uronic acids) were present.

Hydrolysis of the Fraction Soluble in Methyl Iodide.—This polysaccharide derivative was very resistant to methanolysis even on prolonged boiling with fairly high concentrations of hydrogen chloride. Accordingly the methylated polysaccharide (3.9 g.) was dissolved in a solution (50 c.c.) containing glacial acetic acid (2 vols.), concentrated hydrochloric acid (1 vol.), and water (1 vol.) and heated on a water-bath until the rotation was constant (8 hours). The solution was partially neutralised with barium carbonate (to remove all the hydrochloric acid) and filtered, and the filtrate and washings were evaporated to dryness under reduced pressure to remove acetic acid and water. The solid residue was extracted exhaustively with chloroform and the extracts were concentrated under reduced pressure and converted into the methyl glycosides by boiling with methyl alcoholic hydrogen chloride (3%, 7 hours). The resulting methyl glycosides (3.9 g.) were isolated and fractionally distilled giving: Fraction 1 (0.30 g.), b. p. $129/0.001$ mm., $n_D^{20} 1.4495$ (Found: OMe, 54.1%). Fraction 2 (2.45 g.), b. p. $140-160/0.001$ mm., $n_D^{20} 1.4568$ (Found: OMe, 50.7%). Fraction 3 (0.38 g.), b. p. $160-175/0.001$ mm., $n_D^{20} 1.4560$ (Found: OMe, 50.6. Calc. for $C_{10}H_{20}O_6$: OMe, 52.5%). Fraction 4 (0.33 g.), b. p. $175-240/0.001$ mm., $n_D^{20} 1.4686$ (Found: OMe, 41.4%). Still residue (0.44 g.), not further examined.

Examination of the fractions. Fractions 1 and 2 (2.7 g.) were combined and hydrolysed with *N*-hydrochloric acid (20 c.c.) at $90-95^\circ$. $[\alpha]_D^{20} + 20^\circ$ (initial value) $\rightarrow + 81^\circ$ (3 hours, constant value). The solution was cooled, neutralised with barium carbonate, filtered, and concentrated under reduced pressure to a solid which was exhaustively extracted with chloroform. On concentration the extracts gave a syrup (2.4 g.); $n_D^{20} 1.4772$; $[\alpha]_D^{20} + 37^\circ$ (in methyl alcohol) (Found: OMe, 40.9. Calc. for $C_6H_{12}O_6$: OMe, 41.8%). A sample of the syrup (0.039 g.) on dissolving in 3% methyl alcoholic hydrogen chloride (5 c.c.) showed a change of optical rotation identical with that given by 2:3:6-trimethyl *D*-galactose. $[\alpha]_D^{20} + 36^\circ$ (initial value); $+ 8^\circ$ ($8\frac{1}{2}$ hours); $+ 0^\circ$ (14 hours); $- 16^\circ$ (20 hours); $- 26^\circ$ (36 hours, constant value). The sugar (0.89 g.) was dissolved in water (5 c.c.) and bromine (1.5 c.c.) added. The solution was heated to 55° for 4 hours; a test sample after aeration to remove bromine then showed no reduction when heated with Fehling's solution. Bromine and hydrobromic acid were removed and the syrupy 2:3:6-trimethyl *D*-galactonolactone was isolated after removal of solvent at 40° . On standing, the lactone crystallised; it was purified by sublimation in a vacuum; m. p. 92° . Yield, 0.8 g. This product, further purified by recrystallisation from ether-light petroleum, had m. p. and mixed m. p. with an authentic sample, 98° . $[\alpha]_D^{20} - 41^\circ$ in water, initial value (Found: OMe, 41.0; equiv., 220. Calc. for $C_6H_{12}O_6$: OMe, 42.4%; equiv., 220). The lactone was converted quantitatively by solution in liquid ammonia into the amide, m. p. and mixed m. p. with an authentic specimen, 133° .

Fractions 3 and 4 were combined (0.7 g.) and hydrolysed with *N*-hydrochloric acid for 6 hours. The isolated sugars (0.55 g.) gave on oxidation crystalline 2:3:6-trimethyl *D*-galactonolactone, m. p. and mixed m. p. 98° , in 50% yield.

Hydrolysis of the Fraction Insoluble in Methyl Iodide.—A portion of the methylated polysaccharide (4.0 g.) was hydrolysed as described above and the methyl glycosides (4.5 g.) distilled giving: Fraction 5 (0.28 g.), b. p. $115-135/0.001$ mm., $n_D^{20} 1.4532$ (Found: OMe, 50.2%). Fraction 6 (1.59 g.), b. p. $135-145/0.001$ mm., $n_D^{20} 1.4535$ (Found: OMe, 51.4%). Fraction 7 (1.44 g.), b. p. $145-175/0.001$ mm., $n_D^{20} 1.4548$ (Found: OMe, 51.1%). Fraction 8 (0.47 g.), b. p. $175-190/0.001$ mm., $n_D^{20} 1.4588$ (Found: OMe, 49.8%). Fraction 9 (0.33 g.), b. p. $> 190/0.001$ mm., $n_D^{20} 1.4672$ (Found: OMe, 43.5%). Still residue, 0.3 g. (not further examined).

Fractions 5, 6, 7, and 8 had substantially the same constants; they were combined and hydrolysed with *N*-hydrochloric acid for 4 hours ($[\alpha]_D^{20} + 88^\circ$ constant value). The solution was neutralised with

barium carbonate and the sugar isolated (3.5 g.); n_D^{20} 1.4770; $[\alpha]_D^{20} + 36^\circ$ (in methyl alcohol) (Found: OMe, 40.5. Calc. for $C_8H_{10}O_6$: OMe, 41.8%).

A sample of the syrup showed a change of rotation in cold 2% methyl alcoholic hydrogen chloride, similar to that shown by 2:3:6-trimethyl *d*-galactose. $[\alpha]_D^{20} + 36^\circ$ (initial value); $+ 5^\circ$ (24 hours); 0° (36 hours); $- 11^\circ$ (56 hours); $- 26^\circ$ (70 hours, constant value). On oxidation with bromine (1 c.c.) in water (3 c.c.) the syrup (1.04 g.) gave 2:3:6-trimethyl *d*-galactonolactone, m. p. 97° , isolated in 85% yield. $[\alpha]_D^{20} - 41^\circ$ (initial value, in water) (Found: OMe, 41.2; equiv., 220. Calc. for $C_8H_{10}O_6$: OMe, 42.4%; equiv., 222).

A portion of the syrup (0.58 g.) was boiled with aniline (0.3 c.c.) and alcohol (3 c.c.) for 3 hours. On concentration a syrup was formed which crystallised only after 3 months. The crystals were tiled and purified by recrystallisation from absolute alcohol. Yield, 30 mg.; m. p. 189° , not depressed on admixture with an authentic specimen of 2:3:4:6-tetramethyl *d*-galactose anilide. Some 2:3:4:6-tetramethyl *d*-galactose (end group) is therefore present in the sugar syrup. No arabinose derivative could be detected in the products of hydrolysis.

Examination of Polysaccharide Fraction V.—Fraction V, the last fraction from the fractionation of the methylated polysaccharides with light petroleum (b. p. $40-60^\circ$), was purified by extraction with boiling light petroleum. The residual white solid (1.8 g.) [Found: dimethyl pentosan (by furfuraldehyde estimation), 19.4%; OMe, 40%] was subjected to methanolysis with boiling methyl alcoholic hydrogen chloride (3%) for 7 hours. The resulting methylglycosides (1.8 g.) were fractionally distilled giving: Fraction 10 (0.21 g.), b. p. $100^\circ/0.01$ mm., n_D^{20} 1.4355 (Found: OMe, 61%). Fraction 11 (0.24 g.), b. p. $100-120^\circ/0.001$ mm., n_D^{20} 1.4440. Fraction 12 (0.57 g.), b. p. $130-150^\circ/0.01$ mm., n_D^{20} 1.4568.

Fraction 10 (0.21 g.) was hydrolysed with *N*-hydrochloric acid (10 c.c.). $[\alpha]_D^{21} - 47^\circ$ (initial) fell to $- 15^\circ$ (constant value) in 2 hours. The syrupy sugar (0.19 g.) [Found: OMe, 43. Calc. for trimethyl *l*-arabinose ($C_8H_{10}O_6$): OMe, 45.4%], after isolation, was oxidised with bromine (0.3 c.c.) in water (5 c.c.) for $2\frac{1}{2}$ hours at 55° . Bromine was removed by aeration, the solution neutralised with silver carbonate, and the lactone isolated as a sticky solid which was purified on the tile and then by recrystallisation from ether-light petroleum; m. p. 29° , not depressed on admixture with an authentic specimen of 2:3:5-trimethyl *l*-arabonolactone. The lactone on treatment with methyl alcoholic ammonia gave 2:3:5-trimethyl *l*-arabonamide in quantitative yield, m. p. 134° , m. p. 135° on admixture with an authentic specimen of 2:3:5-trimethyl *l*-arabonamide.

The estimated yield of 2:3:5-trimethyl *l*-arabinose was about 8% of Fraction V, approximately one-third of the total pentosan content of the crude methylated polysaccharide. Fraction 11 was not further investigated. Fraction 12 (0.5 g.) on hydrolysis and oxidation (for details see under Fractions 1 and 2) gave 2:3:6-trimethyl *d*-galactonolactone, m. p. 98° , in 80% yield.

Identification of the Acidic Portion of the Polysaccharide as Pectic Acid by Preparation of the Degraded Poly-ester.—The polysaccharide (75 g.) was treated with boiling *N*-sulphuric acid at 90° for 6 hours. This process destroyed the araban and most of the galactan leaving a partly degraded pectic acid which separated as a flocculent precipitate. The insoluble portion (5 g.; equiv., 700) was filtered off and washed free from sulphuric acid, first with water and then with methanol. The solid was then boiled with 2% methyl alcoholic hydrogen chloride for 7 hours, and the insoluble residue was filtered off and washed free from hydrochloric acid with methanol. The solid was purified by dissolving in water and precipitating with ethanol. Yield 3 g. $[\alpha]_D^{20} + 170^\circ$ (in water) (Found: OMe, 17.9; equiv., 210. Calc. for methyl pectate: OMe, 16.3%; equiv., 190). On oxidation a sample gave mucic acid in 46% yield. Pectic acid was therefore a component of the mixture of polysaccharides (A).

The authors wish to thank Imperial Chemical Industries Ltd. for a grant.

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[Received, December 2nd, 1946.]

231. *The Reactions of N-Benzenesulphonylbenzisoctiazolone with Aromatic Amines.*

By (the late) ERNEST W. MCCLELLAND and RAYMOND H. PETERS.

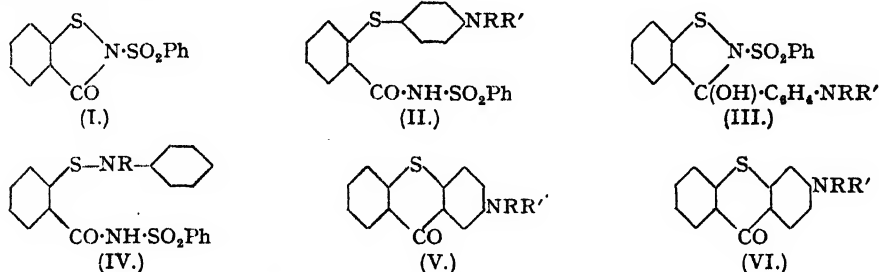
N-Benzenesulphonylbenzisoctiazolone (I) reacts readily with aromatic amines, the hetero-ring being opened and the sulphur atom becoming attached to the *p*-position of the amine to give substances of type (II). Hydrolysis of (II) yields the 4-amino-2'-carboxydiphenyl sulphide, which by the action of sulphuric acid undergoes ring closure to give a 2-amino-thioxanthone (V). When the *p*-position of the aromatic amine is occupied by a substituent R (Me, OMe, or Cl) the sulphur atom becomes attached in the ortho-position relative to the amino-group of the amine and the product isolated is the lactam of the 2-amino-5-R-2'-carboxydiphenyl sulphide (XI), benzenesulphonamide having been eliminated. The lactam yields the free amino-acid on hydrolysis. Sulphuric acid converts these acids into 4-aminothioxanthones (XIII). 2-Amino-2'-carboxydiphenyl sulphide yields a similar lactam when boiled in xylene with phosphoric oxide.

THE reaction of *N*-benzenesulphonylbenzisoctiazolone (I) with aniline had been observed by McClelland and Hart (J., 1939, 760), and preliminary experiments had also been made with dimethylaniline (Barton and McClelland, unpublished observations). In the present

investigation the reactions with a number of aromatic amines have been studied and the nature of the products established.

The benzisothiazolone condenses with one molecular proportion of the amine and several possible formulae were considered for the products, such as (II), (III), and (IV).

The compound from dimethylaniline is converted by heating with sulphuric acid into a dimethylaminothioxanthone. The formation of an aminothioxanthone is compatible with either formula (II) or (III) which would, however, give rise, respectively, to the 2- and 3-dimethylaminothioxanthones (V) and (VI).



2-Dimethylaminothioxanthone (V, R = R' = Me) was synthesised by a variation of Mayer's method (*Ber.*, 1909, 42, 3046) as follows. The action of *p*-dimethylaminothiophenol on diazotised anthranilic acid yielded 4-dimethylamino-2'-carboxydiphenyl sulphide, which was converted by sulphuric acid into the required 2-dimethylaminothioxanthone found to be identical with the substance under discussion above. The condensation product from dimethylaniline is therefore of type (II) and not (III).

Similar results were obtained on using methylethylaniline and benzylmethylaniline, the aminothioxanthone being independently synthesised in the former case.

The product of reaction with monomethylaniline was hydrolysed to an acid which must be (VII) since it gives an acetyl derivative. This excludes formula (IV) for this condensation product, and points to formula (II, R = H, R' = Me). The substance also yields a thioxanthone, which by analogy must be 2-methylaminothioxanthone.

The substance formed by condensation of the benzisothiazolone with aniline is now found to contain a free primary amino-group and is converted by sulphuric acid into 2-aminothioxanthone. This compound therefore has the structure (II, R = R' = H). In the production of the thioxanthones, sulphonic acids of the type (VIII) are also obtained. With *o*-toluidine an analogous condensation occurred.



Benzylamine and phenylhydrazine do not condense with the benzisothiazolone in boiling alcohol, but cause opening of the ring and yield di-*N*-benzenesulphonyl-2:2'-dithiobenzamide.

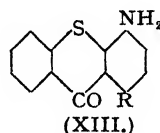
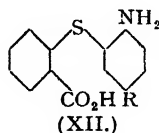
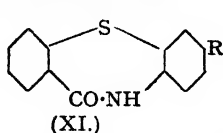
On the other hand when the *N*-benzenesulphonylbzisothiazolone was condensed with para-substituted amines a different reaction occurred, benzenesulphonamide being eliminated. The thiazolone reacted in this manner with *p*-toluidine, *p*-anisidine, and *p*-chloroaniline, but did not react with weaker bases such as the nitroanilines or anthranilic acid. The products were of high melting point and inert to bromine; they gave no colour with ferric chloride, were neither acidic nor basic, and gave no reaction for a keto-group. Their composition corresponded with that of the respective arylisothiazolone (I, C₆H₄X in place of SO₂Ph) or an isomer of it.

N-*p*-Tolylbenzisothiazolone, however, prepared by the action of 2-chlorothiobenzoyl chloride on *p*-toluidine, was found to be an entirely different substance from the condensation product from *p*-toluidine.

In view of the mode of reaction of benzylamine and phenylhydrazine with the benzisothiazolone, mentioned above, the possibility was considered that a disulphide (C₆H₄-S-CO-NHR), had been formed, the difference in composition being negligible. But, again, the disulphide prepared by the action of *p*-toluidine on 2:2'-dithiobenzoyl chloride was entirely different from the product under discussion: moreover the molecular weight of the corresponding substance

resulting from the reaction of *p*-anisidine with the benzothiazolone was not double as would be required for the disulphide.

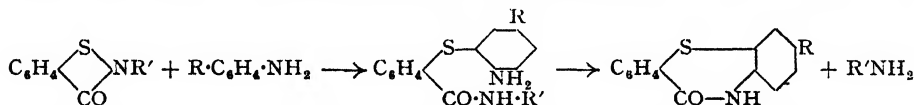
The condensation product yielded a *dioxide* soluble in aqueous sodium hydroxide and reprecipitated unchanged on acidification. Both the condensation product and its dioxide yielded monoacetyl derivatives. These were finally identified as lactams of the structure (XI) since hydrolysis with 55–65% sulphuric acid yielded in each case an aminocarboxylic acid. A thioxanthone is formed at the same time, which is evidently the result of further action of the sulphuric acid on the amino-acid. The acids must have the structure (XII) which should give 4-aminothioxanthenes (XIII). This was confirmed by preparing 4-amino-1-methylthioxanthone from *o*-mercaptobenzoic acid and *p*-toluenesulphon-*p*-toluidide in sulphuric acid (cf. Ullmann and Glenck, *Ber.*, 1916, 49, 2499); the product was identical with the thioxanthone from the amino-acid derived from the condensation product of *p*-toluidine and the benzenesulphonylbenzothiazolone.



The condensation products in question are thus lactams of the amino-acids of type (XII). These acids when heated with alcoholic hydrochloric acid were partly converted into the lactam. Acetic anhydride or phosphoric oxide also regenerated the lactam (XI) together with some of the thioxanthone in the latter case.

The seven-membered ring here present is not unusual in view of the presence of two *o*-phenylene groups, but it was thought desirable to provide the following confirmatory evidence. The parent sulphide, 2-amino-2'-carboxydiphenyl sulphide (Mayer, *loc. cit.*) with phosphoric oxide yielded a corresponding cyclic lactam together with some 4-aminothioxanthone. This was entirely similar in behaviour to the condensation products from *N*-benzenesulphonylbenzothiazolone with para-substituted amines. Oxidation also gave a sulphone of similar properties, and this too was prepared independently from the sulphone of 2-nitro-2'-carboxydiphenyl sulphide.

The reaction of the benzothiazolone with para-substituted amines therefore proceeds thus :



and it follows that the products should be independent of the particular radical *R'* present. This was confirmed by causing the *N*-*p*-toluenesulphonylbenzothiazolone to react with *p*-anisidine; the product was identical with that from *N*-benzenesulphonylbenzothiazolone.

Attempts to bring about reaction between dimethylaniline and *N*-methyl-, *N*-phenyl-, *N*-*p*-tolyl-, *N*-*p*-nitrophenyl-, or *N*-benzoyl-benzothiazolone gave negative results, and it appears that this type of reaction of the arylsulphonylbenzothiazolones depends on the joint action of the SO_2 and CO groups attached to the same nitrogen atom, the simultaneous presence of which facilitates the rupture of the heterocyclic ring.

EXPERIMENTAL.

Reaction of *N*-Benzenesulphonylbenzothiazolone with Tertiary Aromatic Amines.—The benzothiazolone (5 g.) was boiled in alcohol (20 ml.) with the amine (5 g.) until all the former had dissolved (3 hrs.). The product crystallised on cooling. 4-Dimethylamino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide was thus obtained from dimethylaniline, as yellow needles from alcohol, m. p. 172° (Found: C, 61.6; H, 4.7. $\text{C}_{21}\text{H}_{19}\text{O}_2\text{N}_3\text{S}_2$ requires C, 61.1; H, 4.9%). In his examination of this substance Dr. A. W. H. Barton isolated a sodium salt sparingly soluble in water crystallising from alcohol in white needles, m. p. 308° (Found: Na, 5.4. $\text{C}_{21}\text{H}_{18}\text{O}_2\text{N}_3\text{S}_2\text{Na}$ requires Na, 5.3%), and by methylation with methyl sulphate a methyl derivative, white needles from methyl alcohol, m. p. 144° (Found: C, 62.0; H, 5.2. $\text{C}_{22}\text{H}_{21}\text{O}_2\text{N}_3\text{S}_2$ requires C, 62.0; H, 5.2%), which on hydrolysis with acid yielded benzenesulphonmethylamide, m. p. 31°. The original condensation product was hydrolysed by boiling for 2 hours with concentrated hydrochloric acid, and the mixture poured into water, made alkaline with sodium hydroxide, and finally acidified with acetic acid. The greenish precipitate was purified by crystallisation of the sodium salt, reversion into the acid and crystallisation from alcohol; it formed small greenish needles, m. p. 250–260° (decomp.). 4-Dimethylamino-2'-carboxydiphenyl sulphide so obtained was identical with that prepared synthetically as follows. *pp'*-Bisdimethylaminodiphenyl disulphide (10 g.) prepared by the method of Merz and Weith (*Ber.*, 1889, 22, 1571) was reduced by

warming with tin (3 g.) and concentrated hydrochloric acid (30 c.c.), the solution made alkaline (100 c.c. of 35% aqueous sodium hydroxide) and heated while a stream of nitrogen was passed through the flask, and a diazotised solution of anthranilic acid (8.8 g.) slowly added. After 5 minutes' boiling and cooling the grey-green sodium salt which separated was collected and dissolved in water, and the free acid precipitated by adding acetic acid. It was apparently identical with the hydrolysis product described above (Found on a sample from alcohol, dried in a vacuum: C, 64.9; H, 5.7. After drying at 110°: C, 66.4; H, 5.9. $C_{18}H_{15}O_2NS.C_6H_5O$ requires C, 64.0; H, 6.6%. $C_{18}H_{15}O_2NS$ requires C, 66.0; H, 5.5%). The presence of alcohol in the former specimen was confirmed by an iodoform test.

In view of the indefiniteness of the melting point of this substance the *ethyl* ester was prepared from both the hydrolysis product and the synthetic acid. In each case it formed white needles from alcohol, m. p. 143° (not depressed by mixture of the two). For analysis the substance was purified by molecular distillation (Found: C, 67.5, 67.5; H, 6.8, 6.4. $C_{17}H_{13}O_2NS$ requires C, 67.7; H, 6.4%). Other amines yielded the corresponding 4-aminodiphenyl sulphides. 4-Methylethylamino-2'-N-benzenesulphonylcarbamyldiphenyl sulphide formed pale yellow plates from alcohol, m. p. 141° (Found: C, 61.1, 60.6; H, 5.6, 6.0. $C_{22}H_{22}O_2N_2S_2$ requires C, 61.7; H, 5.2. $C_{22}H_{22}O_2N_2S_2.C_2H_5O$ requires C, 61.0; H, 6.0%). On hydrolysis with concentrated hydrochloric acid it yielded 4-methylethylamino-2'-carboxydiphenyl sulphide as a greenish microcrystalline powder, m. p. ca. 230° (decomp.) (Found: C, 66.8; H, 5.9. $C_{16}H_{11}O_2NS$ requires C, 66.8; H, 6.0%). This acid was also synthesised. 4:4'-Bis-methylethylaminodiphenyl disulphide prepared by Merz and Weith's method (*loc. cit.*) formed an amorphous mass which did not crystallise and was used in the crude form. It was reduced to the thiol as described above, and with diazotised anthranilic acid gave the 4-methylethylamino-2'-carboxydiphenyl sulphide as a pale green microcrystalline powder, m. p. ca. 230° (decomp.) (Found: C, 66.8; H, 5.9%). 4-Benzylmethylamino-2'-N-benzenesulphonylcarbamyldiphenyl sulphide crystallised in pale green needles from alcohol, m. p. 123°. The crystals contain alcohol of crystallisation as shown by direct test (Found: C, 65.1; H, 5.2. $C_{27}H_{24}O_2N_2S_2$ requires C, 66.4; H, 4.9. $C_{27}H_{24}O_2N_2S_2.C_2H_5O$ requires C, 65.1; H, 5.6%). Hydrolysis with 60% sulphuric acid yielded 4-benzylmethylamino-2'-carboxydiphenyl sulphide, which crystallised from alcohol as a pale green microcrystalline powder, m. p. 194° (Found: C, 71.7; H, 5.0. $C_{21}H_{19}O_2NS$ requires C, 72.1; H, 5.5%).

4-Methylethylamino-2'-N-benzenesulphonylcarbamyldiphenyl sulphide separated from alcohol in white plates which turned green on exposure to air, m. p. 142° (Found: C, 60.5; H, 4.4. $C_{20}H_{18}O_2N_2S_2$ requires C, 60.3; H, 4.5%). The *nitroso*-derivative crystallised from alcohol in golden needles, m. p. 170° (Found: C, 56.0; H, 4.1. $C_{20}H_{17}O_2N_3S_2$ requires C, 56.1; H, 4.0%). Hydrolysis with 60% sulphuric acid yielded 4-methylamino-2'-carboxydiphenyl sulphide, small needles from butyl alcohol, m. p. 215° (Found: C, 64.9; H, 5.5. $C_{14}H_{13}O_2NS$ requires C, 64.8; H, 5.1%). The *acetyl* derivative formed white plates, m. p. 209° (Found: C, 63.4; H, 5.3. $C_{15}H_{15}O_2NS$ requires C, 63.8; H, 5.0%).

4-Ethylamino-2'-N-benzenesulphonylcarbamyldiphenyl sulphide separated from aqueous alcohol in cream coloured crystals, m. p. 150° (Found: C, 61.0; H, 5.1. $C_{21}H_{20}O_2N_2S_2$ requires C, 61.1; H, 4.9%). The *nitroso*-derivative crystallised from alcohol in small red prisms which turned yellow on heating, m. p. 138° (Found: C, 56.7; H, 4.3. $C_{21}H_{19}O_2N_3S_2$ requires C, 57.1; H, 4.4%). Hydrolysis with 60% sulphuric acid yielded 4-ethylamino-2'-carboxydiphenyl sulphide, which crystallised from butyl alcohol in buff needles, m. p. 224° (Found: C, 65.6; H, 5.4. $C_{15}H_{15}O_2NS$ requires C, 65.0; H, 5.5%). The *acetyl* derivative separated from aqueous alcohol in almost colourless needles, m. p. 184° (Found: C, 64.7; H, 5.4. $C_{17}H_{17}O_2NS$ requires C, 64.7; H, 5.4%).

4-Amino-2'-N-benzenesulphonylcarbamyldiphenyl sulphide, obtained by using aniline, crystallised from aqueous alcohol in small white needles, m. p. 167° (analysed, but incorrectly formulated by McClelland and Hart, *J.*, 1939, 760). The *perchlorate* separated in minute needles from dilute perchloric acid, m. p. 221° (decomp.) (Found: C, 45.3, 45.7; H, 4.1, 4.0. Found after drying at 100°: C, 45.0; H, 3.4. $C_{19}H_{17}O_7N_2ClS_2.H_2O$ requires C, 45.4; H, 3.8%. $C_{19}H_{17}O_7N_2ClS_2$ requires C, 45.4; H, 3.8%). Diazotisation and coupling with alkaline β -naphthol gave the corresponding *azo*- β -naphthol, which crystallised in red prisms from ethyl acetate or acetone, m. p. 148° (Found: C, 64.0, 64.0; H, 4.1, 4.1. $C_{20}H_{19}O_4N_3S_2$ requires C, 64.5; H, 3.9%). The filtered diazo-solution after addition of urea and boiling yielded 4-hydroxy-2'-N-benzenesulphonylcarbamyldiphenyl sulphide, which separated from hot water in small white needles, m. p. 143°. Hydrolysis with 60% sulphuric acid yielded 4-amino-2'-carboxydiphenyl sulphide, which after crystallisation from aqueous alcohol had m. p. 193° not depressed by admixture of an authentic specimen prepared from the nitro-acid obtained from *p*-nitrothiophenol and anthranilic acid (*cf.* Mayer, *loc. cit.*).

Reaction with *o*-toluidine produced 4-amino-2'-N-benzenesulphonylcarbamyldiphenyl-3-methyldiphenyl sulphide, which after purification through the perchlorate crystallised from alcohol in white needles, m. p. 118° (Found: C, 59.7; H, 5.3. $C_{26}H_{25}O_2N_2S_2.C_2H_5O$ requires C, 59.4; H, 5.4%). The *perchlorate* formed cream coloured needles from dilute perchloric acid, m. p. 225° (decomp.) (Found: C, 48.6; H, 4.0. $C_{26}H_{25}O_2N_2ClS_2$ requires C, 48.2; H, 3.8%). The corresponding *azo*- β -naphthol crystallised from ethyl acetate in dark red prisms, m. p. 136° (Found: C, 65.0; H, 4.6. $C_{30}H_{23}O_4N_3S_2$ requires C, 66.1; H, 4.2%).

Action of Sulphuric Acid on the Foregoing Aminodiphenyl Sulphides.—The 4-substituted 2'-N-benzenesulphonylcarbamyldiphenyl sulphides were warmed at 50° for 1 hour with concentrated sulphuric acid (20 c.c. for 5 g.). The resulting solution on being poured into water gave a white precipitate of a sulphonic acid, and addition of alkali to the filtered solution yielded an aminoxanthone, a further yield of which was obtained by redissolving the sulphonic acid in alkali.

2-Dimethylaminothioxanthone crystallised from alcohol in orange needles, m. p. 122° (Found: C, 70.4; H, 5.3; N, 5.7. $C_{18}H_{15}ONS$ requires C, 70.5; H, 5.1; N, 5.5%). The substance gave a green fluorescence in sulphuric acid solution. It was found by m. p. and mixed m. p. to be identical with the xanthone produced by the action of concentrated sulphuric acid on synthetic 4-dimethylamino-2'-carboxydiphenyl sulphide (see above).

The sulphonic acid was purified by precipitation from alkaline solution, redissolved and boiled in

alkali with charcoal, reprecipitated, and finally boiled with water. It was a white microcrystalline powder, m. p. 318°, presumably 4-dimethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid, but the position of the sulphonic acid group was not proved (Found: C, 50.9; H, 4.1; N, 3.6. $C_{18}H_{15}O_6NS_2$ requires C, 51.0; H, 4.2; N, 3.9%). When this substance was heated in concentrated sulphuric acid (10 parts) for $\frac{1}{2}$ hour at 150° a brown solution with green fluorescence was formed. The solution was diluted and made alkaline, the dark red mass deposited was dissolved in water, and the solution was acidified. The acid precipitated was crystallised from hot water and formed a light brown microcrystalline powder not melting at 310°. The substance was hygroscopic and analyses were unsatisfactory, but it was presumably 2-dimethylaminothioxanthone-3-sulphonic acid (Found: C, 49.8; H, 4.3. Found after drying at 100° in a vacuum: C, 51.9; H, 4.5. $C_{18}H_{15}O_6NS_2 \cdot H_2O$ requires C, 51.0; H, 4.3%. $C_{18}H_{15}O_4NS_2$ requires C, 53.7; H, 3.9%). The sodium salt had m. p. 310°; the potassium salt was a dihydrate (Found: H_2O , 6.8. $C_{18}H_{15}O_4NS_2K \cdot 2H_2O$ requires H_2O , 6.8%) and had m. p. 95° or, after heating at 100° in a vacuum, m. p. 230°.

2-Methylethylaminothioxanthone was similarly obtained and crystallised from alcohol in pale orange needles, m. p. 120° (Found: C, 70.9; H, 5.6. $C_{16}H_{13}ONS$ requires C, 71.3; H, 5.6%). This compound was identified by m. p. and mixed m. p. with that obtained by the action of sulphuric acid on synthetic 4-methylethylamino-2'-carboxydiphenyl sulphide (see above).

The accompanying sulphonic acid formed white needles from hot water, m. p. 314° (decomp.), and was 4-methylethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid (Found: C, 52.6; H, 4.6. $C_{18}H_{17}O_6NS_2$ requires C, 52.3; H, 4.6%). The sodium salt had m. p. 272°, the potassium salt m. p. 215°. 2-Benzylmethylaminothioxanthone crystallised from alcohol in yellow needles, m. p. 149.5° (Found: C, 76.2; H, 5.4. $C_{21}H_{17}ONS$ requires C, 76.1; H, 5.2%). 4-Benzylmethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid was a microcrystalline powder sparingly soluble in hot water, m. p. 286° (decomp.) (Found: C, 58.9; H, 4.6. $C_{21}H_{19}O_6NS_2$ requires C, 58.7; H, 4.5%).

2-Methylaminothioxanthone crystallised from aqueous alcohol in small yellow needles, m. p. 158°, or minute red crystals becoming yellow at ca. 144° (Found: C, 70.0; H, 4.5. $C_{14}H_{11}ONS$ requires C, 69.7; H, 4.6%). The accompanying 4-methylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid formed white needles from hot water, m. p. 321° (decomp.) (Found: C, 46.3; H, 4.2. $C_{14}H_{13}O_6NS$ requires C, 46.6; H, 3.8. $C_{14}H_{13}O_6NS \cdot H_2O$ requires C, 47.0; H, 4.2%).

2-Ethylaminothioxanthone was obtained as orange plates or needles from alcohol, m. p. 134° (Found: C, 70.3; H, 5.1. $C_{14}H_{13}ONS$ requires C, 70.5; H, 5.1%). No sulphonic acid was isolated in this case.

2-Amino-1-thioxanthone formed yellow needles from alcohol or plates from nitrobenzene, m. p. 227° (Found: C, 69.3; H, 3.7; N, 4.3. Calc.: C, 68.7; H, 4.0%. Cf. Mayer, *loc. cit.*, who also reports poor analyses). It was shown to be identical with the aminothioxanthone synthesised (in poor yield) by the method of Smiles (*J.*, 1911, 2046) or by that of Mayer (*loc. cit.*).

This substance, boiled with acetic anhydride in toluene solution for 4 hours, yielded a diacetyl derivative which crystallised from toluene in yellow crystals, m. p. 245° (Found: C, 65.3; H, 3.9. $C_{17}H_{13}O_5NS$ requires C, 65.6; H, 4.2%). On hydrolysis it furnished the parent amino-1-thioxanthone.

In its production from the condensation product from aniline it was accompanied by 4-amino-2'-carboxydiphenyl sulphide-3-sulphonic acid, which separated in small white crystals from water, m. p. > 320° (Found: C, 48.0; H, 3.5. $C_{13}H_{11}O_6NS_2$ requires C, 48.0; H, 3.4%).

Reaction of N-Benzenesulphonylbenzothiazolone with p-Substituted Aromatic Amines. Formation of the Lactams of the 2-Amino-2'-carboxydiphenyl Sulphides.—The thiazolone was heated for 5 hours in boiling alcohol with an equal weight of p-toluidine, the solution evaporated to dryness, and the product recrystallised from alcohol or glacial acetic acid. The lactam of 2-amino-2'-carboxy-5-methyldiphenyl sulphide was thus isolated as glistening plates, m. p. 274° (Found: C, 69.2; H, 4.5. $C_{14}H_{11}ONS$ requires C, 69.7; H, 4.6%). Benzenesulphonamide was found in the mother liquors. The lactam was oxidised by hydrogen peroxide in acetic acid to its sulphone, a white microcrystalline powder, m. p. > 320° (Found: C, 61.5; H, 4.1. $C_{14}H_{11}O_5NS$ requires C, 61.4; H, 4.1%). The lactam was hydrolysed by boiling it for 4 hours with 65% sulphuric acid. On dilution a precipitate was formed containing the sulphate of the amino-acid, and a thioxanthone, separated by dissolving the former out in alkali. The residue was 4-amino-1-methylthioxanthone, yellow needles from alcohol, m. p. 183° not depressed by admixture of a specimen prepared by the method of Ullmann and Glenck (*Ber.*, 1916, 49, 2499). The alkaline solution, on acidification with acetic acid, gave a 2-amino-2'-carboxy-5-methyldiphenyl sulphide, which crystallised from butyl alcohol in pale buff needles, m. p. 170° (Found: C, 65.2; H, 5.1. $C_{14}H_{13}O_6NS$ requires C, 64.9; H, 5.1%). The acid was re-converted by boiling in acetic anhydride for $\frac{1}{2}$ hour or by standing overnight in sulphuric acid solution into the lactam, m. p. 271°. The lactam was also formed when the acid was heated for 3 hours in boiling ethyl alcohol containing 2–5% of hydrogen chloride, and the ethyl ester of the acid, m. p. 100°, was also produced. When the acid was heated in boiling xylene for $\frac{1}{2}$ hour with phosphoric oxide it yielded the lactam together with 4-amino-1-methylthioxanthone.

The thiazolone with p-anisidine furnished the lactam of 2-amino-2'-carboxy-5-methoxydiphenyl sulphide, which crystallised from alcohol in white needles, m. p. 235° (Found: C, 64.9; H, 4.1; M, ebullioscopic in alcohol, 250. $C_{14}H_{11}O_2NS$ requires C, 65.3; H, 4.3%; M, 241). The acetyl derivative formed white needles from alcohol, m. p. 165° (Found: C, 63.7; H, 4.6. $C_{16}H_{13}O_3NS$ requires C, 64.2; H, 4.4%). The sulphone separated as a microcrystalline powder from acetic acid, m. p. 246° (Found: C, 58.3; H, 4.2. $C_{14}H_{11}O_4NS$ requires C, 58.1; H, 3.8%), which also yielded an acetyl derivative, m. p. 194° (Found: C, 58.5; H, 4.0. $C_{16}H_{13}O_4NS$ requires C, 58.0; H, 3.9%).

The same lactam was obtained when N-p-toluenesulphonylbenzothiazolone was used in place of the benzenesulphonyl derivative. Hydrolysed by acid it furnished the 2-amino-2'-carboxy-5-methoxydiphenyl sulphide, which crystallised from dilute acetic acid or butyl alcohol in buff needles, m. p. 168° (Found: C, 61.6; H, 4.9. $C_{14}H_{13}O_6NS$ requires C, 61.1; H, 4.8%), and formed a perchlorate, which separated from dilute perchloric acid as a white microcrystalline powder, m. p. 210° (decomp.) (Found: C, 43.3; H, 4.5. $C_{14}H_{14}O_6NCIS \cdot H_2O$ requires C, 42.9; H, 4.1%). As a by-product in the hydrolysis a

substance was isolated which crystallised from glacial acetic acid in red needles, m. p. 238°, and appeared to be 4-amino-1-hydroxythioxanthone (Found : C, 63.0; H, 3.8. $C_{13}H_9O_2NS$ requires C, 63.5; H, 3.8%). The acid kept overnight in sulphuric acid solution yielded 4-amino-1-methoxythioxanthone, yellow plates from alcohol, m. p. 168° (Found : C, 64.9; H, 4.4. $C_{14}H_{11}O_2NS$ requires C, 65.3; H, 4.8%).

The action of *p*-chloroaniline on *N*-benzenesulphonylbenzothiazolone (12 hours' boiling) yielded the lactam of 5-chloro-2-amino-2'-carboxydiphenyl sulphide, which crystallised from glacial acetic acid in colourless plates, m. p. 321° (Found : C, 59.0; H, 3.4. $C_{13}H_9ONClS$ requires C, 59.6; H, 3.1%). Hydrolysis with 65% sulphuric acid gave the acid, which separated from dilute acetic acid as a microcrystalline powder, m. p. 183° (Found : C, 55.1; H, 3.8. $C_{13}H_9O_2NSCl$ requires C, 55.8; H, 3.6%).

Lactam of 2-Amino-2'-carboxydiphenyl Sulphide.—2-Amino-2'-carboxydiphenyl sulphide of m. p. 157° prepared Mayer's method (*loc. cit.*), when heated with phosphoric oxide in boiling xylene for $\frac{1}{2}$ hour, gave the lactam, which crystallised from acetic acid in colourless plates, m. p. 256° (Found : C, 68.4; H, 4.2. $C_{13}H_9ONS$ requires C, 68.7; H, 4.4%). Oxidation with hydrogen peroxide in acetic acid yielded the lactam sulphone, which separated from dilute acetic acid in colourless needles, m. p. 290° (Found : C, 60.4; H, 3.8. $C_{13}H_9O_2NS$ requires C, 60.1; H, 3.5%). These lactams are soluble in warm aqueous sodium hydroxide. The same lactam sulphone was also obtained from 2-nitro-2'-carboxydiphenyl sulphone (Mayer, *loc. cit.*) by reduction to the amino-acid sulphone and heating the latter with phosphoric oxide in xylene.

***p*-Toluidide and *p*-Nitroanilide of Dithiobenzoic Acid.**—2 : 2'-Dithiobenzoyl chloride reacted with *p*-toluidine or *p*-nitroaniline in carbon tetrachloride or toluene solution, yielding the *p*-toluidide, m. p. 233° (Found : C, 69.2; H, 5.1. $C_{23}H_{24}O_2N_2S_2$ requires C, 69.4; H, 5.0%), and the *p*-nitroanilide, which crystallised from aqueous pyridine in light brown needles, m. p. 263° (Found : C, 57.0; H, 3.5. $C_{24}H_{18}O_6N_4S_2$ requires C, 57.1; H, 3.3%).

***N*-Arylbisothiazolones.**—Chlorine was passed into 2 : 2'-dithiobenzoyl chloride (10 g.) covered with carbon tetrachloride (60 c.c.) until it had dissolved, the excess of chlorine removed by a current of nitrogen, and the resulting solution added to an ice-cooled solution of *p*-toluidine (20 g.) in carbon tetrachloride (200 c.c.). The dark solution was filtered and evaporated, and the product crystallised from methyl alcohol (charcoal). *N*-*p*-Tolylbenzothiazolone was thus obtained as colourless needles, m. p. 135° (Found : C, 69.3; H, 4.3. $C_{14}H_{11}ONS$ requires C, 69.7; H, 4.5%). A similar condensation with *p*-nitroaniline using pyridine as solvent yielded *N*-*p*-nitrophenylbenzothiazolone, a microcrystalline powder from acetic acid, m. p. 238° (Found : C, 57.1; H, 3.2. $C_{13}H_9O_2N_2S$ requires C, 57.3; H, 3.0%). This substance was also obtained by adding to the *p*-toluidide of dithiobenzoic acid (3 g.) covered with carbon tetrachloride (50 c.c.) a solution of bromine (2 g.) in carbon tetrachloride (10 c.c.). The dirty red precipitate of bromo-thiol was removed by filtration and boiled with acetic acid (100 c.c.). The thiazolone crystallised on cooling, m. p. 238°. Oxidation by hydrogen peroxide in hot acetic acid converted it into *N*-*p*-nitrophenylsaccharin, pale yellow plates from acetic acid, m. p. 229° (Found : C, 50.8; H, 2.4. $C_{13}H_9O_4N_2S$ requires C, 51.3; H, 2.6%).

The authors wish to thank Dr. A. W. H. Barton for his help with the earlier experiments.

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[Received, November 29th, 1946.]

232. A Method of Synthesis of Trinitromethane Derivatives.

By W. S. REICH and (in part) G. G. ROSE and W. WILSON.

The present investigations have shown that aromatic halogenomethyl derivatives react with the silver salt of *aci*-trinitromethane yielding trinitromethane derivatives. They are stable, crystalline, colourless compounds, most probably of the true nitro-type. The reaction also yields varying amounts of unstable, deeply coloured derivatives, probably of the *aci*-trinitromethane type.

A number of trinitromethyl and polytrinitromethyl derivatives were prepared by this method, all of which contained the trinitromethyl group in the side chain of the benzene nucleus. The benzene nucleus itself was in many cases either nitrated or polynitrated.

Improved or new methods for the preparation of a number of intermediary products are also described.

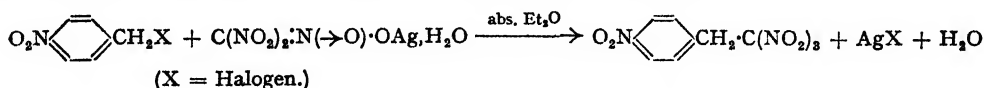
TRINITROMETHANE (nitroform) was first prepared by Schischkoff (*Annalen*, 1857, 101, 216) by the action of water or alcohol on trinitromethyl cyanide, and later several methods for its preparation from tetranitromethane were described (Hantzsch and Rinkenberger, *Ber.*, 1899, 32, 635; Chattaway and Harrison, *J.*, 1916, 109, 171; Macbeth and Orr, *J.*, 1932, 534). A number of addition compounds of trinitromethane, such as its salts with pyridine, piperidine, and dibenzylamine, have also been prepared (Schmidt and Fischer, *Ber.*, 1920, 53, 1529); they are very unstable and soon decompose on keeping.

Two aliphatic trinitromethane derivatives, *viz.*, 1 : 1 : 1-trinitroethane and hexanitroethane, have been described. Franchimont (*Rec. Trav. chim.*, 1886, 5, 282) obtained the former by the action of concentrated nitric acid on methylmalonic acid, and it was later prepared (Hantzsch and Rinkenberger, *loc. cit.*) by reaction between silver trinitromethane and methyl iodide, but

this silver salt and iodotrininitromethane failed to give hexanitroethane. All attempts to use higher halogeno-paraffins, such as ethyl or butyl iodide, instead of methyl iodide, with a view to obtain other trinitromethane derivatives failed to yield any pure or stable compound. Will (*Ber.*, 1914, 47, 963) obtained hexanitroethane by the action of concentrated nitric and sulphuric acids on the potassium salt of 1 : 1 : 2 : 2-tetranitroethane.

Ponzio (*Gazzetta*, 1932, 62, 503) obtained aromatic azo-derivatives of trinitromethane [e.g., $p\text{-Cl}\cdot\text{C}_6\text{H}_4\cdot\text{N}\cdot\text{N}\cdot\text{C}(\text{NO}_2)_3$] by the reaction of ammonium trinitromethane with aromatic diazonium salts. They form yellow or orange crystalline compounds, which rapidly decompose on standing or in solution.

The present investigation has shown that it is possible to prepare stable, crystalline, aromatic trinitromethane derivatives. The synthesis was carried out by reaction of the silver salt of trinitromethane with halogenomethyl derivatives of the aromatic series :



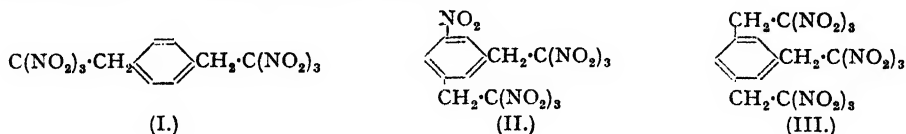
It is noteworthy that the *aci*-trinitromethane group of the silver salt is rearranged to the true nitro-type very probably contained in the stable, colourless trinitromethane derivative. The reaction also yields an unstable, deeply coloured, trinitromethane derivative, probably of the *aci*-trinitro-type, which slowly decomposes with elimination of nitrous fumes. The yield of this unstable compound depends on the working conditions and on the nature of the aromatic group. Substitution of negative groups in the benzene nucleus, especially in the *p*-position, increases the yield of the stable compound.

All the trinitromethane derivatives described in this investigation are very stable : after 3 years' standing in stoppered bottles at room temperature, they showed no change.

(With G. G. ROSE.) The preparation of the 2 : 4 : 6-trinitrobenzyl derivative by the same method proceeds easily, and the yield of the stable compound (presumably of the true nitro-type) is greater (64%) than that of the *p*-nitrobenzyl derivative (45%). In both cases, there was also formed a small amount of an unstable deeply coloured oil, presumably a mono-*aci*-compound or a mixture derived from it by decomposition and secondary reactions.

Attempts to cause reaction between 2 : 4 : 6-trinitrobenzyl bromide and the silver salt of *aci*-trinitromethane were unsuccessful, but the iodide afforded 2 : 4 : 6-trinitro-2' : 2' : 2'-trinitroethylbenzene.

(With W. WILSON.) The same reaction was utilised for the synthesis of some polytrinitromethyl derivatives : *p*-xylylene di-iodide, $\omega\omega'$ -di-iodo-5-nitro-*m*-xylene, and $\omega\omega'\omega'$ -tri-iodo-mesitylene reacted with an ethereal solution of silver *aci*-trinitromethane to yield, respectively, 1 : 4-bis-2' : 2' : 2'-trinitroethylbenzene (I), 5-nitro-1 : 3-bis-2' : 2' : 2'-trinitroethylbenzene (II), and 1 : 3 : 5-tris-2' : 2' : 2'-trinitroethylbenzene (III).



EXPERIMENTAL.

Silver Salt of Trinitromethane.—This preparation has been described by Hantzsch and Rinkenberger (*loc. cit.*), but for the preparation of larger quantities of pure material the following method is better. Silver oxide (freshly prepared, still slightly damp, 265 g.) was cautiously and gradually added to a solution of trinitromethane (180 g.) in ether (1000 c.c.); after each addition the mixture was shaken for a short while, and when the addition was complete the mixture was vigorously shaken over-night. The solution was separated by filtration, and the low-boiling material removed under reduced pressure, the ether at room temperature, and the remaining liquid at 42° (bath temp.)/12 mm. The residue was kept at 42°/12 mm. for an hour after it had crystallised and was then pressed on porous plates. A typical yield was 260 g. (ca. 70%).

***p*-Nitrobenzyltrinitromethane.**—*p*-Nitrobenzyl bromide (85 g.) was dissolved in dry ether (1800 c.c.), the solution stirred in a water-bath at 20°, and a solution of the silver salt of trinitromethane (109 g.) in ether (800 c.c.) gradually added. After the addition was complete, the stirring was continued for about 2 hours and the mixture was left in the water-bath for 48 hours. The precipitated silver bromide was then filtered off, washed with ether, and dried in a desiccator (76 g. Calc. : 75 g.). The filtrate was concentrated in a high-speed evaporation apparatus at 25° (bath temp.)/12 mm., and the residue, consisting of a red liquid and a solid, was left on the vacuum pump at 30° (bath temp.) for about 15 minutes, and then for 2 hours in a refrigerator. The pale pink crystals were separated by filtration and

pressed on a porous plate (51 g., 45%), m. p. 129° (decomp.). The substance was dissolved in 250 c.c. of boiling absolute alcohol, the solution filtered while hot, and the filtrate kept overnight at 0°. The crystals were separated by filtration, washed with a small amount of cold absolute alcohol, and dried in a desiccator (34 g.). The substance was recrystallised from 200 c.c. of hot absolute alcohol-carbon tetrachloride (25:75) (yield 28 g.) and three further similar recrystallisations afforded 17 g. of pure 4-nitro-2':2':2'-trinitroethylbenzene; white crystals, m. p. 135° (Found: C, 33.7; H, 2.3; N, 19.5. $C_8H_6O_6N_3$ requires C, 33.6; H, 2.1; N, 19.6%).

2:4:6-Trinitrobenzyl Bromide.—Ganguly's method (Ber., 1925, 58, 708) was used with some modifications. Repeated crystallisation gave a substance, m. p. 71°, which was almost analytically pure (Found: Br, 26.85. Calc. for $C_7H_4O_6N_3Br$: Br, 26.14%). Ganguly gives m. p. 65° but no analysis.

2:4:6-Trinitrobenzyl Iodide.—Reich, Wetter, and Widmer's method (Ber., 1912, 45, 3056) was used. The brown solid was twice recrystallised from hot methyl alcohol, yielding needles, m. p. 87°; yield 47%. In general, the brominated derivative was only once crystallised before being converted into the iodo-compound, as the latter was then considerably easier to purify.

2:4:6-Trinitro-2':2':2'-trinitroethylbenzene.—Trinitrobenzyl iodide (105.9 g.) and ether (150 c.c.) were stirred whilst a solution of the silver salt of *aci*-trinitromethane (87 g.) in ether (280 c.c.) was added. The stirring was continued for 18 hours and the mixture filtered. The filtrate on evaporation yielded an unstable red oil which was ignored. The residue, a yellow-brown powder (140 g.), was extracted in portions with chloroform (Soxhlet), and the residues from the extraction were powdered and re-extracted with chloroform. On cooling, the chloroform extracts yielded a light brown, crystalline solid (72 g., 64%), m. p. 151.5–152.5° (decomp.). [The residue insoluble in chloroform was silver iodide (65 g. Calc.: 70 g.).] The brown crystals (72 g.) were dissolved in hot ethyl acetate (220 c.c.), the solution filtered from traces of silver iodide, chloroform (500 c.c.) added to the fairly warm filtrate, and the mixture cooled to 0°; the yellow crystals obtained (62 g.), m. p. 152.5–153.5° (decomp.), were four times recrystallised from hot ethyl nitrate-chloroform (1:1 by vol.), and the pure *hexanitro*-compound isolated as faintly coloured, large crystals (38 g.), m. p. 153–154° (decomp.) (Found: C, 25.8; H, 1.3; N, 22.4. $C_8H_4O_{12}N_6$ requires C, 25.5; H, 1.1; N, 22.35%).

Before each crystallisation the substance was finely powdered with an agate pestle and mortar and then dissolved with stirring in the requisite quantity of hot ethyl nitrate (about 150 c.c. to 55 g. of substance); when solution was complete an equal volume of chloroform was added, and the mixture cooled to 0° until crystallisation was complete. By this means prolonged heating, which caused extensive discolouration, was avoided.

ω-Bromo-5-nitro-*m*-xylene.—5-Nitro-*m*-xylene (2 g.) in boiling ethylene dibromide (40 c.c.) was irradiated by a 100-watt tungsten-filament lamp whilst a solution of bromine (4.3 g.) in ethylene dibromide (15 c.c.) was dropped in. After an hour the bromination was complete. Removal of the ethylene dibromide at 75°/20 mm. yielded a dark semi-solid substance, which was recrystallised from petroleum (b. p. 40–60°); yield, 500 mg. of *ω*-bromo-5-nitro-*m*-xylene, m. p. 59.5–60° (Found: C, 9.4; H, 3.4. $C_8H_8O_2NBr$ requires C, 41.7; H, 3.5%).

ωω'-Dibromo-5-nitro-*m*-xylene.—5-Nitro-*m*-xylene (m. p. 71–72.5°; 120 g.), dissolved in boiling ethylene dibromide (450 c.c.), was heated under reflux and irradiated with a 500-watt tungsten-filament lamp whilst a solution of dry bromine (100 c.c.) in ethylene dibromide (100 c.c.) was added fairly rapidly. After the bromine had almost disappeared, the ethylene dibromide was removed in a vacuum, the residue allowed to crystallise, and the crystals separated and washed with ether. Recrystallisation from petrol (b. p. 80–100°) yielded pure *ωω'*-dibromo-5-nitro-*m*-xylene (46 g.), m. p. 105–106.5° (Found: Br, 51.4. $C_8H_6O_2NBr_2$ requires Br, 51.8%).

Both the mono- and the di-bromo-compound were lachrymatory and had skin-irritant properties, and both afforded silver bromide quantitatively on treatment with warm aqueous-alcoholic silver nitrate.

ωω'-Di-iodo-5-nitro-*m*-xylene.—The crude dibromo-compound (above) (62 g.) was added to a solution of sodium iodide (85 g.) in acetone (400 c.c.); after 1 hour's heating under reflux the acetone was distilled off, and the residue washed with water. The product, crystallised from benzene-petroleum (b. p. 40–60°), yielded 53 g. of pure *ωω'*-di-iodo-5-nitro-*m*-xylene, m. p. 136–137° (Found: N, 3.6. $C_8H_6O_2NI_2$ requires N, 3.5%).

5-Nitro-1:3-bis-2':2':2'-trinitroethylbenzene.—(i) *ωω'*-Dibromo-5-nitro-*m*-xylene (m. p. 102–105°; 8 g.) was suspended in ether (100 c.c.) and 48.8 c.c. of a solution of the silver salt of trinitromethane (containing 297.4 g. per l. of ether) were added slowly. After 3 days, the silver bromide (10 g.) was filtered off, the filtrate washed with water, and then desolvated at 30°/20 mm.; the semi-solid residue was triturated with chloroform at 0°, yielding crystals (0.9 g.), m. p. 158–160°. Recrystallisation from chloroform yielded the pure *heptanitro*-compound, m. p. 170–171.5° (slight decomp.) (Found: C, 26.6; H, 1.8; N, 21.8. $C_{10}H_2O_{14}N_7$ requires C, 26.7; H, 1.6; N, 21.8%).

(ii) *ωω'*-Di-iodo-5-nitro-*m*-xylene (50 g.) was suspended in dry ether (500 c.c.), and 280 c.c. of an ethereal solution of the silver salt of trinitromethane (containing 248 g. per l.) were added fairly rapidly at 18–25° with vigorous stirring. After the stirring had continued for 4 hours, the silver iodide (61 g.) was filtered off, and the filtrate washed with water and dried (Na_2SO_4). The ether was removed in a vacuum, and the residue triturated with a little chloroform at 0° and the solution filtered after 15 minutes. The product was separated by filtration and washed on the filter with chloroform, yielding a pale pink solid (29 g.), m. p. 160–165° (decomp.). Recrystallisation from chloroform (charcoal) yielded the *heptanitro*-compound (22 g.), m. p. 171–172° (decomp.) (Found: C, 26.5; H, 1.65; N, 21.7%).

p-Xylylene Di-iodide.—This was prepared from the dichloride by double exchange with sodium iodide in acetone solution, the dichloride having been made by chloromethylation of benzyl chloride (Stephen, Short, and Gladding, *J.*, 1920, 117, 510; Quelet, *Bull. Soc. chim.*, 1933, 53, 222). Recrystallised from benzene-ethanol, the di-iodide had m. p. 179.5–180° (Found: C, 26.9; H, 2.0. Calc. for $C_8H_6I_2$: C, 26.8; H, 2.2%). Grimaux (*Compt. rend.*, 1870, 70, 1365; *Annalen*, 1870, 155, 341) gives m. p. 170°; Finkelstein (Ber., 1910, 43, 1532), m. p. 174°.

1:4-Bis-2':2':2'-trinitroethylbenzene.—*p*-Xylylene di-iodide (5 g.) was suspended in dry ether

(100 c.c.) and 27 c.c. of a solution of the silver salt of trinitromethane (containing 303.5 g. per l., in ether) were added slowly. After 2 hours' stirring and a further 15 hours' standing, the silver iodide (7 g. Calc. : 6.6 g.) was filtered off, the filtrate washed with water, dried, and desolvated at 30°/20 mm.; the pale yellow semi-solid product was triturated with a little chloroform on a sintered-glass filter, yielding a solid (0.6 g.), m. p. ca. 165° (decomp.). Recrystallisation from chloroform yielded white needles of the *hexanitro*-compound, m. p. 190° (decomp.) (Found : C, 29.7; H, 2.3; N, 20.6. $C_{10}H_2O_{12}N_6$ requires C, 29.7; H, 2.0; N, 20.8%).

ωω'ω''-Tri-iodomesitylene.—*ωω'ω''-Tribromomesitylene* (m. p. 98–99°; 1.5 g.) was added to a solution of sodium iodide (3.0 g.) in acetone (30 c.c.); after 30 mins.' heating under reflux, most of the acetone was distilled off, and the residue washed with water and dried, yielding *ωω'ω''-tri-iodomesitylene* (2.1 g.), m. p. 131–133°; crystallised from benzene, needles, m. p. 133° (Found : C, 22.6; H, 1.9. $C_9H_3I_3$ requires C, 22.1; H, 1.9%).

1 : 3 : 5-*Tris*-2' : 2' : 2'-*trinitroethylbenzene*.—*ωω'ω''-Tri-iodomesitylene* (5.5 g.) was suspended in ether (100 c.c.) and 34 c.c. of a solution containing 287 g. of the silver salt of trinitromethane per l. of ether were added fairly rapidly. After 2 hours' stirring, the product was allowed to stand overnight. The silver iodide (7.3 g. Calc. : 7.8 g.) was filtered off, and the solution washed with water to remove unchanged silver nitroform [the amount of which was determined by conversion into silver chloride (1.3 g.), showing that the reaction was probably about 80% complete]. The ethereal solution was dried and desolvated at 30° in a vacuum, yielding a brown oil mixed with crystals. Trituration with chloroform yielded a white solid (550 mg.), m. p. 198–200° (decomp.). Two crystallisations from chloroform yielded the required *nitro*-compound (250 mg.), m. p. 205–206° (decomp.) (Found : C, 25.4; H, 1.72; N, 22.23. $C_{12}H_9O_{15}N_9$ requires C, 25.4; H, 1.59; N, 22.22%).

This work was carried out during 1941–1944 in the Department of Scientific Research, Inter-Services Research Bureau, The War Office. The authors wish to express their thanks to the Director of the Department, Professor D. M. Newitt, F.R.S., for his interest and invaluable support. Their thanks are also due to the Director General of Scientific Research (Defence) for the permission to publish these investigations.

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[Received, November 30th, 1946.]

233. The Reaction of Benzoic Anhydride with Aromatic Compounds Catalysed by Boron Trifluoride.

By P. H. GIVEN and D. LL. HAMMICK.

Boron trifluoride catalyses the interaction in nitrobenzene solution of benzoic anhydride with aromatic compounds to give ketones. Phenyl 1-naphthyl ketone, phenyl 2-hydroxy-1-naphthyl ketone, and phenyl 2-thienyl ketone are formed by reaction of the acid anhydride with naphthalene, 2-naphthyl methyl ether, and thiophen respectively. The same catalyst is effective in the Fries rearrangement of 2-naphthyl benzoate.

IN 1939–1940 we initiated a programme of work on the acylation of aromatic compounds with benzoic and other anhydrides in the presence of boron trifluoride, but were unable to complete it. We therefore record here the results of the work as far as we were able to carry it.

Meerwein and Vossen have reported (*J. pr. Chem.*, 1934, **141**, 149) the interaction of acetic anhydride with benzene and other aromatic compounds in the presence of boron trifluoride to give aryl methyl ketones, but do not mention the use of any other acid anhydrides. Their experimental procedure involved the saturation of the mixed reactants at 0° with the catalyst, followed by warming till all the fluoride was given off again. The yield of some ketones was decreased by intermolecular condensations of the acetic anhydride to give β-diketones. Bowlus and Nieuwland (*J. Amer. Chem. Soc.*, 1931, **53**, 3835) state that benzoic and phthalic anhydrides (in an unspecified solvent) do not absorb boron trifluoride, but that benzoic acid in chloroform takes up the gas, forming an insoluble complex.

We have found that benzoic and phthalic anhydrides in nitrobenzene, and the former in carbon tetrachloride and in tetrachloroethane, react with boron trifluoride, depositing solid complexes. The weight of gas taken up, after allowing for its solubility in the solvent, was approximately equivalent to 2 moles of BF_3 per mole of anhydride.

For our acylation experiments we chose nitrobenzene as solvent, on the grounds that the reaction presumably resembles the Friedel–Crafts reaction in being ionic in nature (see Linstead, *Ann. Reports*, 1937, 251; Price and Ciskowski, *J. Amer. Chem. Soc.*, 1938, **60**, 2499), and therefore should proceed most readily in a solvent of high dielectric constant.

By reaction of benzoic anhydride with thiophen we obtained a 40% yield of phenyl 2-thienyl ketone; a dirty residue, non-volatile in steam, was also formed. 2-Naphthyl methyl ether gave 55% of phenyl 2-hydroxy-1-naphthyl ketone; complete demethylation occurred.

Phenyl naphthyl ketone (77% crude product) was obtained by reaction of benzoic anhydride with naphthalene; after three crystallisations, substantially pure phenyl 1-naphthyl ketone was obtained (about 60%). Price and Ciskowski (*loc. cit.*) in the reaction of benzyl alcohol with naphthalene in the presence of boron trifluoride, also found the 1-isomer to predominate.

It was found that (under the conditions used in the benzoylations) boron trifluoride catalysed the Fries rearrangement of 2-naphthyl benzoate; a 34% yield of pure phenyl 2-hydroxy-1-naphthyl ketone was obtained.

In order to confirm the reasoning which led to the choice of nitrobenzene as solvent for the reaction mixture, an attempt was made to acylate naphthalene with benzoic anhydride in carbon tetrachloride solution. Under the same conditions as were used in the reaction in nitrobenzene only 4% of crude phenyl naphthyl ketone was obtained. Benzoic acid in reaction with naphthalene and boron trifluoride in nitrobenzene solution gave no phenyl naphthyl ketone.

The procedure used here appears to be unnecessarily vigorous for the benzoylation of reactive substances such as thiophen, as is shown by the formation of tarry by-products. The benzoylation of naphthalene by this method gives a rather higher yield of phenyl 1-naphthyl ketone, and the product is less contaminated with the 2-isomer than that of the Friedel-Crafts reaction of benzoyl chloride with naphthalene, catalysed by aluminium chloride (see, for example, Caille, *Compt. rend.*, 1911, 153, 393); the necessary time of reaction is less (24 hours as against 3 days).

EXPERIMENTAL.

(Melting points are corrected.)

Materials.—Naphthalene, benzoic acid, and benzoic anhydride were dried in a vacuum desiccator before use. Solvents were dried with calcium chloride and redistilled. Boron trifluoride was prepared by the method of Krause and Nitsche (*Ber.*, 1921, 54, 2786). A mixture of boric oxide, potassium borofluoride, and concentrated sulphuric acid was heated slowly from 135° to 250°. The gas was passed through a spray trap, but was not purified in any other way.

Absorption of Boron Trifluoride by the Reactants.—Experiments were carried out in test tubes fitted with side tubes. These, with inlet tube, rubber connections and clips were weighed empty and with the liquid before and after absorption. The liquid was cooled in ice during absorption. Absorption was allowed to proceed to constant weight. These experiments were made primarily to determine whether the acid anhydrides did or did not absorb boron trifluoride, and high accuracy is not claimed.

The data are presented in the Table. In column 4 the solubility of the gas in the solvent or solution is given in g. per 100 g. of solvent. In column 5 the molar ratio, boron trifluoride to benzoic acid or anhydride, is given.

Absorption of Boron Trifluoride.

Solute.	Solvent.	Wt. of solute per 100 g. of solvent.	Solubility, g./100 g.	Ratio, moles BF ₃ / moles acid or anhydride.
None.....	Nitrobenzene	—	17.6	—
None.....	Tetrachloroethane	—	9.8	—
Benzoic anhydride	Nitrobenzene	12.6	24.4	1.8
Benzoic anhydride	Tetrachloroethane	7.87	15.0	2.2
Phthalic anhydride	Nitrobenzene	10	26.3	1.9

Benzoylation Experiments.—The reactants and solvent were placed in a three-necked flask, which was fitted with an inlet tube, mechanical stirrer, and calcium chloride tube. The stirrer was of the glass link type, and was run very fast so as to break up the surface of the liquid. A mercury-sealed stirrer was used in some experiments, but a simple well-fitting glass sleeve was found quite satisfactory. The inlet tube was bent so that the gas was delivered in the liquid, directly under the stirrer. An excess of boron trifluoride (3–5 moles per mole of benzoic anhydride) was passed in the course of 1–2 hours according to the scale of experiment. During absorption of boron trifluoride the flask was cooled in ice. After absorption, the reaction mixture was stirred and kept at 0° for 3–4 hours, and then left, while slowly warming to room temperature, for a further 18 hours. It was then shaken with dilute sodium hydroxide solution, and the solvent and any excess reactants were removed in steam. The product was obtained either from the steam distillate or from the residue by extraction.

Phenyl 2-thienyl ketone. Benzoic anhydride (2 g.) and thiophen (1 c.c.) in nitrobenzene (12 g.) were treated with excess of boron trifluoride, and the product was worked up as above. The ketone distilled in steam after the solvent had been removed; it was extracted from the distillate with ether and dried, and the ether was removed; 0.7 g. of brownish crystals was obtained. After 2 crystallisations from light petroleum (b. p. 60–80°) the compound had m. p. 52°.

Phenyl 2-hydroxy-1-naphthyl ketone from 2-naphthyl methyl ether. Benzoic anhydride (4 g.) and 2-naphthyl methyl ether (2.5 g.) in nitrobenzene (18 g.) were treated with excess of boron trifluoride as above. From the residue of the steam distillation, 2.5 g. (70%) of crude ketone were obtained, completely soluble in warm sodium hydroxide solution. Crystallised from ligroin and twice from 60% alcohol, it gave fine yellow needles, m. p. 140–140.5°.

Phenyl 1-naphthyl ketone. (a) Benzoic anhydride (22.6 g.), naphthalene (12.8 g.), and nitrobenzene (140 c.c.) were treated with about 23 g. of boron trifluoride (*i.e.*, about 3 moles per mole of benzoic anhydride). From an ether extract of the residue from the steam distillation, 19 g. (77%) of crude

phenyl naphthyl ketone were obtained. A solution of 0.3 g. in 1 c.c. of benzene gave no precipitate after being boiled for 2 minutes and kept for 15 hours with 0.2 g. of picric acid in 1 c.c. of benzene (the 2-isomer gives an insoluble picrate in benzene, the 1-isomer none, and a mixture can be separated by virtue of this fact; see Perrier and Caille, *Compt. rend.*, 1908, **146**, 769). The remainder of the crude product was crystallised 3 times from dilute alcohol, with charcoal; m. p. 73—74° (Perrier and Caille, *loc. cit.*, give 76°).

(b) Naphthalene (4.3 g.) and benzoic anhydride (7.5 g.) in carbon tetrachloride (75 c.c.) were treated with excess of boron trifluoride; a copious white precipitate was thrown down. About 2.8 g. of unchanged naphthalene were found in the steam distillate. From the residue 0.3 g. (about 4%) of crude phenyl naphthyl ketone was obtained.

Attempted reaction of benzoic acid with naphthalene. Benzoic acid (5 g.) and naphthalene (5 g.) in nitrobenzene (65 c.c.) were treated with boron trifluoride as above. The materials were recovered substantially unchanged, and no phenyl naphthyl ketone was detected.

Fries Rearrangement of 2-Naphthyl Benzoate.—Naphthyl benzoate (7 g.) in nitrobenzene (65 c.c.) was treated with a large excess (about 15 g.) of boron trifluoride as above. The residue from the steam distillate was made strongly alkaline, and filtered hot from some black solid. The filtrate was made acid and filtered again. The residue on the filter was crystallised twice from dilute alcohol with the addition of charcoal. The product was phenyl 2-hydroxy-1-naphthyl ketone (2.4 g., 34%), m. p. 140.5—141°.

Our thanks are due to Imperial Chemical Industries Ltd. for a grant.

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[Received, December 3rd, 1946.]

234. *The Reduction of Oxides by Hydrogen and Carbon Monoxide.*

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The previous investigations on the heats of adsorption of hydrogen, carbon monoxide, oxygen, and carbon dioxide on ZnO , $\text{MnO}_{1.4}$, Cr_2O_3 and their mixtures have been summarised. These oxides are semi-conductors and there is considerable mobility of ions in the oxide lattice at the temperature of reduction. The adsorption at room temperature takes place on a surface which may be the result of an equilibrium set up in a lattice defect structure at higher temperatures.

Reversible chemisorption of carbon monoxide occurs on metal-rich oxides with negative holes, and irreversible chemisorption on oxides with positive holes. The two types of chemisorption are not readily interconvertible. The reversible adsorption of carbon monoxide on zinc oxide, and the adsorption of carbon dioxide on the oxides of the transition elements occur without appreciable activation energy. It is suggested that when carbon monoxide is adsorbed irreversibly, there is set up a resonating system involving the *S* and *D* shells of the transition element. This system is moved in the direction of the carbonate ion, when the stoichiometric quantity of oxygen is adsorbed on the surface. The ease with which the carbonate ion is dissociated is thus determined by the number of unpaired electrons in the *D* and *S* shells of the transition element.

INVESTIGATIONS on the reduction of metallic oxides by hydrogen and carbon monoxide have shown that the reaction proceeds through a number of intermediate stages to yield hydroxides and carbonates which decompose to produce the lower oxide or metal (Garner and Kingman, *Trans. Faraday Soc.*, 1931, **27**, 322; Garner and Veal, *J.*, 1935, 1436, 1487; Dowden and Garner, *J.*, 1939, 894; Garner and Ward, *J.*, 1939, 858; Ward, following paper). The processes which precede the evolution of water or carbon dioxide include (a) van der Waals adsorption, which is specially predominant at low temperatures, and also (b) several types of chemisorption. The rate of chemisorption on oxides increases rapidly with increase of temperature, which led Taylor (*J. Amer. Chem. Soc.*, 1931, **53**, 578) to designate this type of process as "activated" adsorption. The heats of chemisorption of carbon monoxide and hydrogen on a number of oxides range from 15 to 70 k.-cals./mol., according to the oxide. It is found that if the heat of adsorption is below 20 k.-cals./mol., the gas can be desorbed unchanged on raising the temperature, but when the heat is greater than this value, the adsorption is usually irreversible, in the sense that, on warming, carbon dioxide or water is evolved. The results have been obtained on oxides which are reducible with difficulty. They may, however, be capable of application to easily reduced oxides, where the various stages in the reaction may proceed too quickly for them to be readily isolated from one another.

Chemisorption of Carbon Monoxide and Hydrogen.—In Table I are summarised the heats of adsorption of the two gases on a number of oxides at room temperature. On zinc oxide, carbon monoxide is adsorbed reversibly and carbonates are not formed, the activation energies and heats of reaction being unfavourable for the formation of carbonates in this case. For a mixture of zinc and chromium oxides, the adsorption of hydrogen or carbon monoxide is partly reversible and partly irreversible, the proportion of the two types of chemisorption depending on the state

TABLE I.

Heats of adsorption (in k.-cals./mol.) of CO and H₂ on oxidised and on reduced surfaces.

Substance.	H ₂ .		CO.		Remarks.
	Reduced.	Oxidised.	Reduced.	Oxidised.	
ZnO	No appreciable adsorption		20	18 → 13	Reversible desorption of CO at room temp.
Cr ₂ O ₃	36	72	29 → 22	28 → 12	Hydrogen very difficult to remove, even by long treatment at 450°; CO evolved as CO ₂ at 70—400°.
MnO _{1.5}	44	30	67	62	
ZnO, Cr ₂ O ₃	13 → 10	48 → 13	15 → 11	44 → 16	Partial desorption of CO and H ₂ at room temp.
MnO _{1.5} , Cr ₂ O ₃ ...	No appreciable adsorption		33	47	CO not desorbed at room temp.

of reduction of the oxide. On heating the oxide on which hydrogen or carbon monoxide is reversibly chemisorbed to 100—200°, the gas is evolved unchanged. The pressure rises to a maximum and then falls to zero. On further heating to 400° the gas is evolved as water or carbon dioxide respectively. It is clear that the direct conversion from reversible to irreversible chemisorption does not occur, since the surface reaction is hindered by a high potential energy barrier which is greater than the heat of desorption of the gas (see Fig.). This may be due to the two states of adsorption taking place on different centres. For the other oxides quoted in Table I, the adsorption is, for the most part, irreversible.

Formation of Carbonates.—Information relevant to the formation of carbonates on the surface of the oxides is given in Table II. The oxides were treated with oxygen at 450°, then evacuated and cooled to room temperature. Measurements were made of the heats of adsorption of carbon monoxide, oxygen, and carbon dioxide, and of mixtures of carbon monoxide and oxygen.

When the carbon monoxide is adsorbed irreversibly, carbon dioxide can be liberated on raising the temperature, but it is difficult to desorb this gas at room temperature. On the other hand, if carbon dioxide is adsorbed on the oxide, the heat of formation of the carbonate is of the order of 20 k.-cals., and the gas can be usually desorbed at room temperature, at a rate given by the Polanyi-Wigner equation, $r = \nu \cdot N e^{-Q/RT}$, where Q is the heat of adsorption, N is the number of molecules adsorbed on 1 cm.² of the surface, and $\nu = 10^{13}$ sec. The absence of appreciable activation energy in the formation and dissociation of carbonates is in agreement with the conclusions of Zawadzki and Bretsznajder (*Z. Elektrochem.*, 1935, 41, 215) and Spencer and Topley (*J.*, 1929, 2633). It is, however, clear that when carbon monoxide is adsorbed on an oxide, the product differs in some way from the carbonate formed from carbon dioxide.

TABLE II.

Heats of adsorption (in k.-cals./mol.) of CO and $\frac{1}{2}$ O₂ on oxidised surface.

1.	2.	3.	4.	5.	6.	7.
Substance.	CO.	$\frac{1}{2}$ O ₂ after CO.	CO + $\frac{1}{2}$ O ₂ .	CO ₂ .	Total heat.	$\frac{1}{2}$ O ₂ on reduced surface.
ZnO	18	—	—	13	—	—
Cr ₂ O ₃	29	55	84 †	18	66	40—50
	61 *	38 *	—	—	—	—
MnO _{1.5}	67	24	82	23	68(59)	31
ZnO, Cr ₂ O ₃	44(18)	22	66	15	51	22
MnO _{1.5} , Cr ₂ O ₃ ...	47.	39	85	20	65	52 *
						19

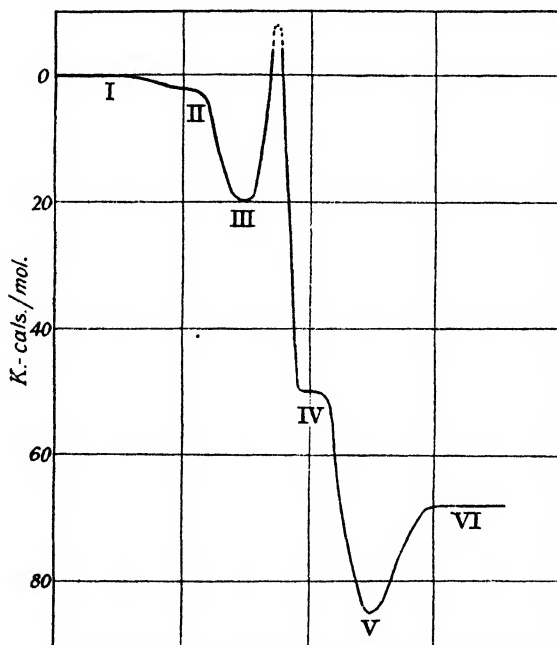
* Oxide containing hydrogen as hydroxide.

† Calculated.

The surface after adsorption of carbon monoxide (col. 2) is, however, unsaturated with respect to oxygen, and a quantity of oxygen can be taken up with the liberation of the heats shown in col. 3. These heats are quite large and depend on the previous history of the oxide as well as on its nature. For Cr₂O₃ the heats are lower if hydrogen is present in the oxide. The observations made with MnO_{1.5}, Cr₂O₃ are instructive. The adsorbed carbon monoxide cannot be removed by evacuation at room temperature, but after the adsorption of oxygen or after the adsorption of CO + $\frac{1}{2}$ O₂ (col. 4), carbon dioxide is liberated on evacuation with a heat of desorption equal to the heat of adsorption of carbon dioxide (col. 5). In order to produce a carbonate from carbon monoxide with the same properties as that formed from carbon dioxide,

it is necessary to reoxidise the surface with the stoichiometric quantity of oxygen. It will be noted that the total heats given in col. 6 correspond in most cases with the heat of the reaction, $\text{CO} + \frac{1}{2}\text{O}_2 \longrightarrow \text{CO}_2$, which provides a good check on the accuracy of the measurements.

Formation of Hydroxides.—The position with regard to the formation of hydroxides is not so clear, since the results at room temperature were not sufficiently complete. "Activated" adsorption of hydrogen does not readily occur on some of the oxides at room temperature. It was shown, however, in a number of cases that the surface reduced with hydrogen was not unsaturated to the same extent as with carbon monoxide. Also, the hydrogen adsorbed irreversibly is so tightly held that it is difficult to remove it completely without sintering the oxide. Thus no information could be obtained with regard to the heat of desorption of water. For Cr_2O_3 , the hydrogen cannot be completely removed, even at 450° . It can, however, be removed in the course of the reduction by carbon monoxide, which mobilises the adsorbed hydrogen. The residual hydrogen in the case of Cr_2O_3 is found to increase materially the heat of adsorption of carbon monoxide.



The reduction of oxides by carbon monoxide.

Energy Levels.—The energy levels formed during the reduction of the oxides are set out schematically in the figure. This only gives a very approximate representation of the results of Table II, since the position of the levels varies with the oxide. The levels from left to right are: I, $\text{CO} + \frac{1}{2}\text{O}_2$; II, van der Waals adsorption of CO; III, reversible chemisorption of CO; IV, irreversible adsorption of CO, leading to an unsaturated surface; V, adsorption of $\text{CO} + \frac{1}{2}\text{O}_2$; and VI, carbon dioxide. There is an activation energy between II and III and carbon monoxide may be desorbed unchanged on raising the temperature if this activation energy is greater than the heat of desorption. This is the case for the adsorption of carbon monoxide on $\text{ZnO}, \text{Cr}_2\text{O}_3$. The overall change from I to VI is the conversion of carbon monoxide and oxygen into carbon dioxide.

Lattice Irregularities.—These oxides belong to the class of semiconductors, the electrical conductivity being due to a defect or excess of some ion in the lattice. Zinc oxide dissolves zinc, giving negative holes in the lattice. Oxides of manganese give a series of partially miscible solid solutions of MnO , Mn_2O_3 , and Mn_3O_4 , which can only be produced at the expense of some lattice irregularity. In this case, oxygen is in excess, which probably gives rise to positive holes in the lattice. It is thus similar to the cuprous oxide, which has been thoroughly investigated by Wagner (cf. Mott and Gurney, "Electronic Processes in Ionic Crystals", 1940), who shows that there is considerable mobility of the ions at high temperatures. On removal of oxygen by

reduction, negative holes will be produced on the surface, and if the temperature is sufficiently high, these negative holes will migrate into the interior of the lattice, their place on the surface being taken by oxygen ions. The surface reduction of oxides might therefore at sufficiently high temperature lead to a movement of oxygen from the interior of the lattice to the surface.

A phenomenon of this type possibly occurs at 450°, when the oxides are undergoing reduction. The extent to which the reduction occurs at this temperature and the quantities of gas which can be absorbed on the reduced surface are shown in Table III.

TABLE III.
Reduction of surfaces of oxides.

Substance.	Wt., g.	Gas used in reduction.	Vol. of gas used up at 400—450°.	Gases adsorbed on reduced surface at saturation, in c.c. at room temp.			Remarks.
				H ₂ .	CO.	O ₂ .	
ZnO, Cr ₂ O ₃	14.8	H ₂	200	3.0	1.4	9.0	Zn volatilises on reduction
ZnO	6.0	H ₂	3 c.c./hr.	V. small	0.35	—	
MnO _{1.5}	11.2	{ CO H ₂	64 243	— 0.17	2.0 —	— —	
Cr ₂ O ₃	16.1	CO	57	V. small	32.3	30.0	
MnO _{1.5} , Cr ₂ O ₃ ...	19.7	CO	28	V. small	1.0	0.10	

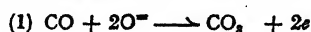
If the surfaces are reduced stepwise, only a relatively slow change in the character of the surface occurs as the reduction proceeds. Thus with ZnO, Cr₂O₃ the reduction by 50 c.c. of hydrogen out of a total possible of 200 c.c. made no significant difference to the volume of hydrogen adsorbed or to its heat of adsorption at room temperature. A similar result also was obtained with MnO_{1.5}; the adsorption and heat of adsorption of carbon monoxide was not appreciably affected by the partial reduction of the oxide. Also, the amount of oxygen adsorbed and the heat of adsorption of oxygen on Cr₂O₃ only increases slowly as the surface is reduced. The amount of oxygen adsorbed by manganous-chromic oxide is only slightly affected by the reduction process. As oxygen is removed from the surface during the reduction, there is evidently some compensating factor which keeps the properties of the surface unchanged. This may well be the diffusion of oxygen ions from the lattice to the surface.

At room temperature the mobility of the oxygen ions within the lattice is probably very low, so that the oxide under these conditions would be expected to be a frozen form of the equilibrium set up at higher temperatures. The adsorption of hydrogen and carbon monoxide at room temperature may therefore take place on lattice irregularities caused by the establishment of equilibrium in a lattice defect structure at higher temperatures. The bearing of lattice defects on the reduction of oxides and for catalysis generally has not yet received much attention, and no researches appear to have been directed specifically to clear up this point.

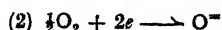
Activation Energy during the Reduction of Oxides.—Carbon monoxide is adsorbed on oxide surfaces in two ways, (1) reversibly and (2) irreversibly. The first type occurs on ZnO, on ZnO, Cr₂O₃, and only to a small extent on the other oxides. On zinc oxide the heat of adsorption is 18 k.-cals. and the gas can be completely desorbed at room temperature within 20 minutes. The rate of desorption is given by $Nve^{-E/RT}$, where N = number of adsorbed molecules per cm.², v = 10^{13} as a maximum value, and E = the energy required to evaporate the molecule from the surface. Calculation shows that E is approximately the same as the heat of adsorption within a few calories. The reversible adsorption is thus not appreciably activated.

On ZnO, Cr₂O₃, both types of adsorption occur, but the passage from reversible to irreversible adsorption does not readily occur on the surface. On heating, carbon monoxide first evaporates and then condenses to give an adsorption complex from which carbon dioxide can be liberated. It is very probable, therefore, that different centres are involved in the two types of adsorption process.

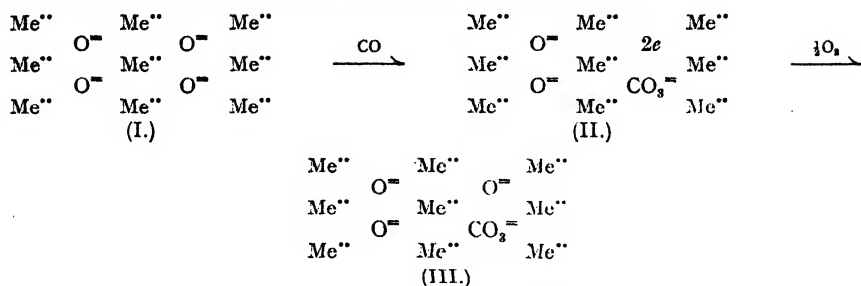
On oxides of the transition elements and their mixtures, carbon monoxide reacts with two oxygen ions or atoms on the surface to give CO₃²⁻ ions, liberating two electrons:



The surface has become unsaturated with respect to oxygen, which can be added in stoichiometric quantities, viz., $\frac{1}{2}\text{O}_2$ to each CO:



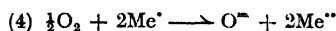
The process is shown schematically below for a bivalent metal ion.



The following qualitative picture can be given in explanation of the experimental results. The electrons set free in (II) will be held in the neighbourhood of the carbonate ion. They will possibly be accommodated in the *S* or *D* shells of the transition element,* which, together with the CO_3^{2-} ion, can form a resonating system :

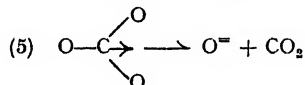


The addition of $\frac{1}{2}\text{O}_2$ in (III),



will have the effect of moving the resonating system in (3) to the right, *i.e.*, in the direction of the formation of CO_3^{2-} ion, which would explain the observation that CO_2 is evolved more readily from state (III) than from state (II).

The carbonate ion can be dissociated to give carbon dioxide. Measurements of the rates of desorption show that within a few calories the activation energy is the same as the heat of adsorption. The process of dissociation involves the displacement of the carbon atom as in (5), and the transference of the two electrons to an oxygen atom and the metal ions associated



with it in the lattice. An activation energy might be expected for this step, but it may be small,† especially if there is some choice among the levels of the *D* and *S* shells of the transition element, in the formation of the bond between the oxygen ion and the surrounding metal ions. If there is a broad band of electronic levels in the shells of the transition element, which are suitably placed with respect to the levels of the oxygen and carbonate ions, then the electron transfer reactions (3)–(5) would be facilitated. The effectiveness of the transition metals for catalysis generally may depend on a suitable distribution of the electron levels in the catalyst.

When carbon monoxide is adsorbed reversibly on zinc oxide, the surface does not become unsaturated with respect to oxygen, and no additional oxygen can be adsorbed after carbon monoxide. This is in accord with the view that reversible and irreversible adsorption of carbon monoxide occur on different centres.

Conclusions on the Reaction of Carbon Monoxide with Oxides.—It has been demonstrated that reversible adsorption of carbon monoxide occurs on metal-rich oxides with negative holes in the lattice, and irreversible adsorption on oxides defective in metal ion with positive holes. The two types of adsorption are not readily inter-convertible and probably occur on different types of centre. Reversible chemisorption may take place on sites where electrons can be donated to the adsorbed molecule, and irreversible adsorption on sites which can abstract electrons from the molecule. The reversible adsorption is not appreciably "activated".

It is suggested that the resonating system $\text{CO} + 2\text{O}^- + 2\text{Me}'' \rightleftharpoons \text{CO}_3^{2-} + 2\text{Me}''$ may play an important part in the irreversible adsorption. The carbon monoxide is held in an intermediate state on the way to a CO_3^{2-} ion. This system will move to the right if the number of unpaired electrons in the shells of the metal ion is increased, so that the extent to which the

* The transition elements are most effective as catalysts when their magnetic susceptibility is highest, indicating that the unpaired electrons in the *D* shell play an important part in heterogeneous catalysis (Hüttig, *J. Amer. Chem. Soc.*, 1935, **57**, 2470; Hofer, Peebles, and Dieter, *ibid.*, 1946, **68**, 1953; Selwood, Hill, and Boardman, *ibid.*, p. 2055).

† I am indebted to Dr. F. C. Frank for this suggestion.

carbonate ion is formed can be increased by the adsorption of oxygen simultaneously with carbon monoxide, $\frac{1}{2}\text{O}_2 + 2\text{Me}^+ \longrightarrow \text{O}^{2-} + 2\text{Me}^+$. This is in accord with the fact that the carbonate ion is more readily dissociated when the surface is saturated with oxygen.

The dissociation of the carbonate ion has been shown to possess an activation energy approximately equal to the heat of adsorption of carbon dioxide, so that the formation of carbonate ions from carbon dioxide requires no appreciable activation energy. In explanation of this fact, it is suggested that the activation energy for the dissociation may be small if the electronic levels of the shells of the metal ions lie in a broad band which is suitably placed with respect to the electronic levels of the oxygen and carbonate ions.

I am indebted to Imperial Chemical Industries Ltd. for a grant for the purchase of apparatus used in these researches.

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[Received, December 8th, 1946.]

235. Heat of Adsorption of Gases on Manganous-Chromic Oxide at Room Temperature.

By T. WARD.

Measurements have been made of the heats of adsorption of carbon monoxide, carbon dioxide, and oxygen. Carbon monoxide is irreversibly adsorbed, giving carbon dioxide on rise of temperature. The surface, after the addition of carbon monoxide, is unsaturated with respect to oxygen. The evolution of carbon dioxide is facilitated after the unsaturation has been removed, and carbon dioxide can be desorbed with a heat of desorption equal to the heat of adsorption of carbon dioxide. The adsorption of carbon dioxide is not "activated".

This investigation is a continuation of a series of experiments on the heats of adsorption of carbon monoxide, carbon dioxide, oxygen, and hydrogen on the metallic oxides, ZnO , $\text{MnO}_{1.5}$, and Cr_2O_3 , and the changes in adsorptive properties that occur on mixing two of the oxides (Garner and Veal, *J.*, 1935, 1436, 1487; Garner and Kingman, *Trans. Faraday Soc.*, 1931, 27, 322; Dowden and Garner, *J.*, 1939, 894; Garner and Ward, *ibid.*, p. 858). In the present work, a study has been made of the heats of adsorption of the above gases on the fully oxidised, reduced, and partly reduced surfaces of manganous-chromic oxide. Particular attention has been paid to the formation of carbonates from carbon monoxide and oxygen, and from carbon dioxide.

Although the properties of Cr_2O_3 and MnO_2 as promoters are well known, little attention appears to have been paid to the study of adsorption on the mixed oxides. Taylor and Williamson (*J. Amer. Chem. Soc.*, 1931, 53, 2168) have shown that over the range -78.5° to 144° there are two forms of adsorption of hydrogen and carbon monoxide. At -78.5° hydrogen was adsorbed molecularly with a heat of 1.9 k.-cals./mol., as calculated from adsorption isotherms. At $300-400^\circ$, the heat of adsorption of hydrogen was ~ 20 k.-cals. Only qualitative results were obtained with carbon monoxide.

EXPERIMENTAL.

Preparation of the Oxide.—Manganous ammonium chromate was prepared by the method of Taylor and Williamson (*loc. cit.*) by the interaction of manganous nitrate and ammonium chromate, the solution being titrated until just neutral with ammonia and then filtered. The precipitate was washed thoroughly with ammonium nitrate solution, then with distilled water, and finally dried. It was now oxidised at 400° in a stream of oxygen for 48 hrs., a black amorphous powder being formed. The powder was unsuitable for use in the type of calorimeter employed; hence, it was pressed into small tablets by means of a pastel press, these tablets being then cut into squares 0.1 mm. in size. It was finally treated *in situ* with oxygen at 400° . No information concerning the X-ray structure of the spinel could be obtained.

Specific Heat of the Oxide.—This was determined by the method employed by Garner and Randall (*J.*, 1924, 125, 881). The average value for the determination was 0.166 cal./deg.

Calorimeter.—This was of the type 1f (Garner and Veal, *loc. cit.*), but with the slight alterations mentioned by Garner and Ward (*loc. cit.*), where the details of the method of measurement are given. The weights of the materials used were, platinum 1.6506 g., Pyrex 2.4023 g., oxide 19.680 g., and the specific heats 0.0314, 0.20, and 0.166 cal./deg. respectively. These values gave a water equivalent of the calorimeter of 3.800 cal./deg.

The calibration of the calorimeter was carried out by noting the change in temperature by a standardised Beckmann thermometer when the temperature of the calorimeter fluid was altered by the addition of either ice or hot water, and at the same time recording photographically the e.m.f. of the thermocouple on a Z.c. Kipp and Zonen galvanometer. The sensitivity was 15 cm. per degree.

A preliminary series of experiments showed that the heat conductance of the catalyst was good; the admission of helium as a diluting gas and the mixing of the oxide with gold wire (Garner and Dowden, *loc. cit.*) were therefore unnecessary. The cooling correction was determined after saturating the oxide with oxygen, carbon dioxide, etc., at pressures of 10^{-4} – 10^{-2} cm., allowing the system to come to equilibrium, and then reducing the temperature of the calorimeter by 1° or 2° . The change in e.m.f. of the thermocouple was recorded, and the loss of temperature per minute for a difference of temperature of 1° between the calorimetric fluid and the thermocouple was obtained for every minute up to the 20th. The values obtained were, 1–8 mins., 0.020° ; 6–10 mins., 0.018° ; 10–15 mins., 0.016° ; 15–20 mins., 0.015° . These values were independent of the gas used, and held over a range of pressures from hard vacuum to 10^{-2} cm. In the following experiments the pressure was not allowed to rise above 10^{-2} cm.

There was no drift with time in the values of the heats of adsorption, except in a few experiments where slow reactions occurred, showing that a uniform distribution of gas was attained throughout the calorimeter.

For most of the work the oxide was reduced by carbon monoxide at 400° . Hydrogen was not employed in the reduction until the end of the experiments, in order to avoid contamination of the solid with hydrogen in the initial experiments.

Adsorption of Oxygen.—28 c.c. of carbon monoxide were required to reduce the surface, and beyond this point the reduction was so slow as to be noticeable only after several days. The extent of the reduction was determined by freezing out and measuring the volume of the carbon dioxide formed. The results for the heats of adsorption on the oxidised, reduced, and partly reduced surface are given below. The last value was obtained on a surface reduced with hydrogen. The partly reduced surface gave lower values for the heat of adsorption than either the fully oxidised or the fully reduced surface.

Reduction of surface (c.c. of CO).	Oxygen adsorbed (c.c.).	Heat of adsorption (k.-cals.).	Reduction of surface (c.c. of CO).	Oxygen adsorbed (c.c.).	Heat of adsorption (k.-cals.).
0	0.2	22 *	18	0.03	— 4.6 †
4	0.045	— 6.6 †	28	0.09	+19.1
8	0.10	— 6.0 †	30 (H ₂)	0.08	+52

* After oxidation at 400° .

† The adsorption on the partially reduced surface was abnormal. The galvanometer showed an immediate absorption of heat, recorded above, followed by a slow positive evolution. The negative values were not due to the presence of temperature gradients in the oxide, since the addition of helium before the experiments gave no change in temperature.

Adsorption of Carbon Dioxide.—The oxidised surface adsorbed 1.8 c.c. of carbon dioxide at a pressure of 10^{-2} cm. For the measurements of heats of adsorption, the gas was admitted 0.6 c.c. at a time and a heat of 20 k.-cals. was obtained for the first admission and 14 k.-cals. for the second. All of the gas could be desorbed on evacuation at room temperature, and the heat of desorption after the first admission gave 19 k.-cals. The rate of desorption was measured, and the Polanyi-Wigner equation, $\text{rate} = N\nu e^{-Q/RT}$, applied, the symbols are as defined in the preceding paper. If Q is calculated from the rate, a value of 22 k.-cals. is obtained for the heat of desorption. On the fully reduced surface the heat of adsorption of carbon dioxide was lower: 0.5 c.c. gave 14 k.-cals. The heat of desorption of this gas was 13 k.-cals. These results show that very little activation energy is needed for the adsorption of carbon dioxide, in agreement with the majority of the results in previous papers.

Adsorption of Hydrogen.—No hydrogen could be adsorbed on the oxidised or reduced surfaces at room temperature, although at 400° the catalyst could be readily reduced. Neither was there any appreciable adsorption of hydrogen when the gas was mixed with oxygen. This is in agreement with the experiments of Taylor and Williamson (*loc. cit.*), who did not obtain appreciable "activated" adsorption of hydrogen below 100° .

Adsorption of Carbon Monoxide, followed by Oxygen.—The carbon monoxide was adsorbed on the oxidised surface, and oxygen admitted subsequently to the same surface. The quantity of oxygen adsorbed was always less than the stoichiometric proportion given by the ratio $\text{CO} : \frac{1}{2}\text{O}_2$. Three series were carried out:

Gas.	C.c. adsorbed.	Heat of adsorption (k.-cals.).	Total (k.-cals.).	Gas.	C.c. adsorbed.	Heat of adsorption (k.-cals.).	Total (k.-cals.).
CO	0.602	46 }	85	CO	0.682	48 }	80
O ₂	0.132	78 }		O ₂	0.168	64 }	
CO	0.546	45 }	83				
O ₂	0.113	76 }					

Carbon monoxide could not be desorbed from the oxide at room temperature until the oxygen had been adsorbed, whereupon it could be completely desorbed as carbon dioxide with a heat of 22 k.-cals. This is the same as the heat of adsorption of carbon dioxide on the oxide surface, so that it is clear that the same adsorption state has been reached from carbon monoxide and oxygen as was obtained with carbon dioxide.

If the surface was saturated previously with 1.81 c.c. of carbon monoxide, only about 0.19 c.c. of oxygen was adsorbed, with a heat of 76 k.-cals., which was the same as that given in the above table, but in this case the heat was liberated slowly and was not completely evolved until 20 mins. had elapsed. This indicates that adsorbed oxygen is undergoing a slow reaction with the surface. On desorption, the carbon dioxide was evolved at room temperature with a heat of 20 k.-cals.

A mixture of $\text{CO} + \frac{1}{2}\text{O}_2$ was admitted to the oxidised surface (0.4 and 0.8 c.c. respectively) and completely adsorbed. A heat of 85 k.-cals. was liberated, which is in agreement with the total heat

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in the above table. The heat of desorption of carbon dioxide in this case was 18 k.-cals., which is within a few calories the same as the heat of adsorption of carbon dioxide.

On the surface reduced with 28 c.c. of carbon monoxide, carbon monoxide was adsorbed with a heat of 33 k.-cals. (0.7 c.c. adsorbed).

DISCUSSION.

The measurements of the heats of adsorption on the mixed oxide, $\text{MnO}_{1.5}\text{Cr}_2\text{O}_3$, and the two oxides separately do not bring to light any phenomena which might be said to characterise promoter action. The research has only been concerned with measurements at one temperature. For the study of promoter action, measurements need to be made over a range of temperatures, in order to cover adequately the range at which chemisorption occurs. At room temperature, the slight adsorption of hydrogen on the separate oxides, and negligible adsorption on the mixed oxides, make it impossible to obtain much information about promoter action in so far as the adsorption of hydrogen is concerned.

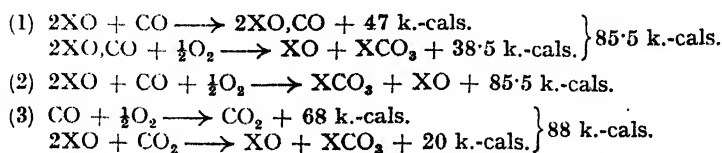
It has become evident as the work proceeded that measurements were giving information on the reduction of oxides by hydrogen and carbon monoxide. This aspect of the results will be dealt with in a separate communication. This discussion will be limited to aspects more specifically derived from the results in the present paper.

It is a striking fact that, for both manganous oxide and manganous-chromic oxide, the reduction of the surface at 400° does not materially increase the quantities of oxygen which can be taken up at room temperature. This is in marked contrast with the behaviour of ZnO , Cr_2O_3 and Cr_2O_3 , where there is an increase on reduction of the quantities of oxygen adsorbed. These differences in behaviour are very probably due to differences in the mobility of the constituents of the lattice at the temperature at which the reduction is carried out. Too little is known about these movements in the case of these oxides to warrant an attempt at a very precise interpretation. The oxides belong to the semi-conductor class for which there is an appreciable electrical conductivity due to lattice defects. A possible interpretation of the results with manganous oxide and manganous-chromic oxide is that the oxygen ions are mobile at the temperature of reduction and that the effects of reduction of these oxides are made good by the diffusion of oxygen from the lattice to the surface at which reduction occurs.

When an oxide is reduced with hydrogen, it is difficult to remove the last traces of water. These materially affect the heats of adsorption, as was pointed out previously in the paper on Cr_2O_3 . A hydrogen-reduced surface of manganous-chromic oxide gives a greater heat of adsorption of oxygen than a carbon monoxide-reduced surface. The heat obtained approaches that given when oxygen is adsorbed on a surface containing carbon monoxide. The high heat may thus be due to lattice defects caused by the presence of hydroxyl ions in the lattice.

The results obtained with carbon monoxide and carbon dioxide are perhaps of the greatest interest, since they can be interpreted unequivocally. Carbon dioxide is adsorbed on manganous oxide, manganous-chromic oxide, and chromic oxide to give carbonates without the necessity for activation energy. The heat of desorption is the same as the heat of adsorption, and the rate of desorption can be calculated from the Polanyi-Wigner equation.

When carbon monoxide is adsorbed on the oxidised surface, the product formed cannot be dissociated at room temperature, and carbon dioxide is evolved only after the temperature is raised. The surface is, however, unsaturated after the adsorption of carbon monoxide, and can take up oxygen. When the unsaturation has been removed, carbon dioxide can be desorbed by evacuation at room temperature. The same final state is produced, whether starting from carbon dioxide or from carbon monoxide, provided in the latter case that oxygen be added at the same time. This is made clear by the following data derived from the heats of adsorption:



The agreement between the heats for the three processes shows that a carbonate is produced in the reaction of carbon monoxide and oxygen with the oxide.

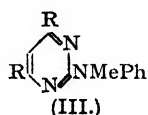
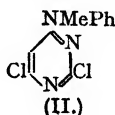
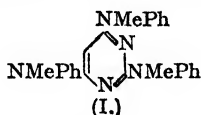
The author wishes to acknowledge the receipt of a grant from Imperial Chemical Industries, Ltd., for the purchase of apparatus.

236. The Constitution of a By-product from the Preparation of Trichloropyrimidine from Barbituric Acid.

By F. E. KING, T. J. KING, and P. C. SPENSLEY.

The constitution of a high-boiling crystalline by-product from the reaction between barbituric acid, phosphoryl chloride, and dimethylaniline is shown by synthesis to be 4 : 6-dichloro-2-*N*-methylanilinopyrimidine and not the expected 2 : 6-dichloro-4-*N*-methyl compound.

WHEN preparing 2 : 4 : 6-trichloropyrimidine from barbituric acid by the improved method of Baddiley and Topham (*J.*, 1944, 679), using phosphoryl chloride and dimethylaniline, a crystalline by-product was isolated from the residue, after distillation of the trichloro-compound, as a fraction of b. p. 240—300°. The yield of recrystallised product averaged 5%, and it was at first believed to be a partly chlorinated barbituric acid. However, analyses indicated the structure to be that of a dichloropyrimidine containing a monomethylaniline residue, thus suggesting either 4 : 6-dichloro-2- or 2 : 6-dichloro-4-*N*-methylanilinopyrimidine as the correct constitution. The by-product was still obtained even when dimethylaniline carefully freed



from traces of the monomethyl compound was employed, and its formation is therefore similar to that of 2 : 4 : 6-tri-*N*-methylanilinopyrimidine (I) from trichloropyrimidine and dimethylaniline (Kawai and Miyoski, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1931, 16, 20), in which the loss of methyl chloride from an intermediate quaternary salt is involved.

Since the action of aniline on trichloropyrimidine is presumed to give 2 : 6-dichloro-4-anilinopyrimidine (Winkelmann, *J. pr. Chem.*, 1927, 115, 305), the constitution of the new pyrimidine was thought to be analogous. This supposition was, however, disproved when the condensation of monomethylaniline and trichloropyrimidine in ethanol gave the non-identical 2 : 6-dichloro-4-*N*-methylanilinopyrimidine (II). Its 2-methylanilino-isomer (III, R = Cl) was therefore synthesised from α -phenyl- α -methylguanidine and ethyl malonate in alcoholic sodium ethoxide solution, the intermediate *N*-methylanilinodihydroxypyrimidine (III, R = OH) giving on treatment with phosphoryl chloride a product indistinguishable from the substance under investigation.

By means of the phosphoryl chloride-dimethylaniline method, 4 : 6-dichloro-5-*p*-chlorobenzeneazo-2-methylpyrimidine has been prepared from the corresponding dihydroxypyrimidine (Lythgoe, Todd, and Topham, *J.*, 1944, 3151), but under similar conditions the 2 : 4 : 6-trihydroxy-5-*p*-chlorobenzeneazo-compound gave only tarry products.

EXPERIMENTAL.

2 : 6-Dichloro-4-*N*-methylanilinopyrimidine.—Methylaniline (11 g., 2 mol.) was added to a solution of trichloropyrimidine (9.2 g., 1 mol.) in ethanol (40 c.c.) at room temperature. After 3 hours the colourless product was collected and crystallised from alcohol. The *dichloromethylanilinopyrimidine* (II) separated in tiny prisms, m. p. 106—107° (Found : C, 51.7; H, 3.8; Cl, 27.8. $C_{11}H_{11}N_3Cl_2$ requires C, 52.0; H, 3.5; Cl, 27.9%).

2-*N*-Methylanilino-4 : 6-dihydroxypyrimidine.— α -Phenyl- α -methylguanidine hydrochloride (8 g.) dissolved in ethanol (20 c.c.) was added to a solution of sodium (2 g.) in ethanol (40 c.c.), and, with the addition of ethyl malonate (6.3 g.), the mixture was heated under reflux on a steam-bath for 8 hours. After standing overnight, the precipitated sodium salt was collected and treated with dilute acetic acid. Crystallisation of the product from boiling water gave the *pyrimidine* (III, R = OH) (2.5 g.) as nearly colourless flat prisms, m. p. 219° (Found : C, 60.8; H, 4.9; N, 19.5. $C_{11}H_{11}O_2N_3$ requires C, 60.8; H, 5.0; N, 19.4%).

4 : 6-Dichloro-2-*N*-methylanilinopyrimidine.—(a) The colourless distillate obtained from the residue of the trichloropyrimidine preparation was crystallised from alcohol, and the *pyrimidine* (III, R = Cl) obtained in thick rhombic plates, m. p. 92—93° (Found : C, 52.0; H, 3.6; Cl, 27.6. $C_{11}H_9O_2Cl_2$ requires C, 52.0; H, 3.5; Cl, 27.9%).

(b) The dihydroxypyrimidine (III, R = OH) (2 g.) was heated under reflux with phosphoryl chloride (6 c.c.) for 15 minutes. The liquid was then poured on ice, and the precipitated solid collected and crystallised from ethanol (Found : C, 53.4; H, 3.8%). Admixture of the product with a specimen from the trichloropyrimidine preparation did not depress its m. p. of 92°.

4 : 6-Dichloro-5-*p*-chlorobenzeneazo-2-methylpyrimidine.—A mixture of 4 : 6-dihydroxy-5-*p*-chlorobenzeneazopyrimidine (5 g.), phosphoryl chloride (6 c.c.), and dimethylaniline (3 c.c.) was warmed until the solid dissolved. The black liquid was poured on ice, and after 1 hour the resinous product was separated by decantation and triturated with alcohol. Crystallisation of the orange solid (2.9 g.,

47%) from ethanol afforded the *azopyrimidine hemi-alcoholate* as clusters of bright red needles, m. p. 104° (Found: C, 44.7; H, 3.1. $C_{11}H_7N_4Cl_2 \cdot \frac{1}{2}EtOH$ requires C, 44.3; H, 3.1%).

2:4:6-Trihydroxy-5-p-chlorobenzeneazopyrimidine (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—A cold aqueous solution of barbituric acid (15 g.) was treated with a solution of *p*-chlorobenzenediazonium chloride (from 15 g. of *p*-chloroaniline) in excess of concentrated hydrochloric acid. The solid which separated on basification with sodium hydrogen carbonate was collected, washed, and dried at 100° ; the very sparingly soluble *azopyrimidine* crystallised from cyclohexanone in minute yellow needles, m. p. 300° (Found: C, 45.0; H, 2.7. $C_{10}H_7O_3N_4Cl$ requires C, 44.9; H, 2.6%). The action of phosphoryl chloride-dimethylaniline on the azo-derivative gave an uncrystallisable resin.

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[Received, September 13th, 1947.]

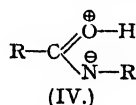
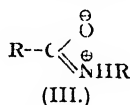
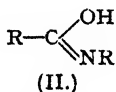
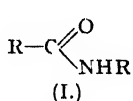
237. Spectroscopic Studies of the Amide Linkage.

By R. E. RICHARDS and H. W. THOMPSON.

The infra-red absorption spectra of a number of simple and substituted amides have been measured between 2 and 15μ . The regions of particular interest are $5-7\mu$ and 3μ , where absorption bands characteristic of the amide grouping occur. There are significant alterations in the spectra according to the state of aggregation in which the substance is measured, and these have an important bearing upon the interpretation of the results. A satisfactory explanation of the positions and shifts of the bands has been given. It is concluded that the amides exist predominantly in the ketonic form, which associates in the solid state through N-H...O bridges. The results provide a basis for more detailed studies on complex amides, amino-acids, and peptides.

THE correlation of the infra-red absorption spectra of simple molecules with the presence of particular structural groups has recently made it possible to apply the method successfully in studying polymers and macro-molecules. It is natural to enquire whether information can be obtained in this way about the structure of proteins, and other compounds in which the amide linkage forms an essential part. We have already obtained some promising results with nylon 66 and its derivatives, and new experimental methods suggest fresh possibilities for the infra-red examination of proteins. Other workers have also explored the subject (Wright, *J. Biol. Chem.*, 1939, 127, 137; Buswell and Gore, *J. Physical Chem.*, 1942, 46, 575). It remains certain, however, that before any detailed understanding of these more complicated molecules is achieved, much must first be explained about the spectra of simple amides and amino-acids.

The conventional plausible structures for an amide are the keto- (I; R = H) and the enol (II; R = H) form. Each of these structures would probably be stabilized by resonance with



a dipolar form, such as (III; R = H) or (IV; R = H). Hantzsch (*Ber.*, 1931, 64, 661) measured the ultra-violet absorption spectra of amides in various solvents, and concluded that in the cases studied—trichloroacetamide and benzamide—the enolic form predominates. On the other hand, more recent X-ray measurements by Senti and Harker (*J. Amer. Chem. Soc.*, 1940, 62, 2008) show that in the solid state these molecules are associated into ring polymers, and that the occurrence of the enolic form is very unlikely. Some infra-red measurements by Buswell, Rodebush, and Roy (*ibid.*, 1938, 60, 2444), by Buswell, Downing, and Rodebush (*ibid.*, 1940, 62, 2759), and by Buswell and Gore (*J. Physical Chem.*, 1942, 46, 575) have been described, but the results are not conclusive.

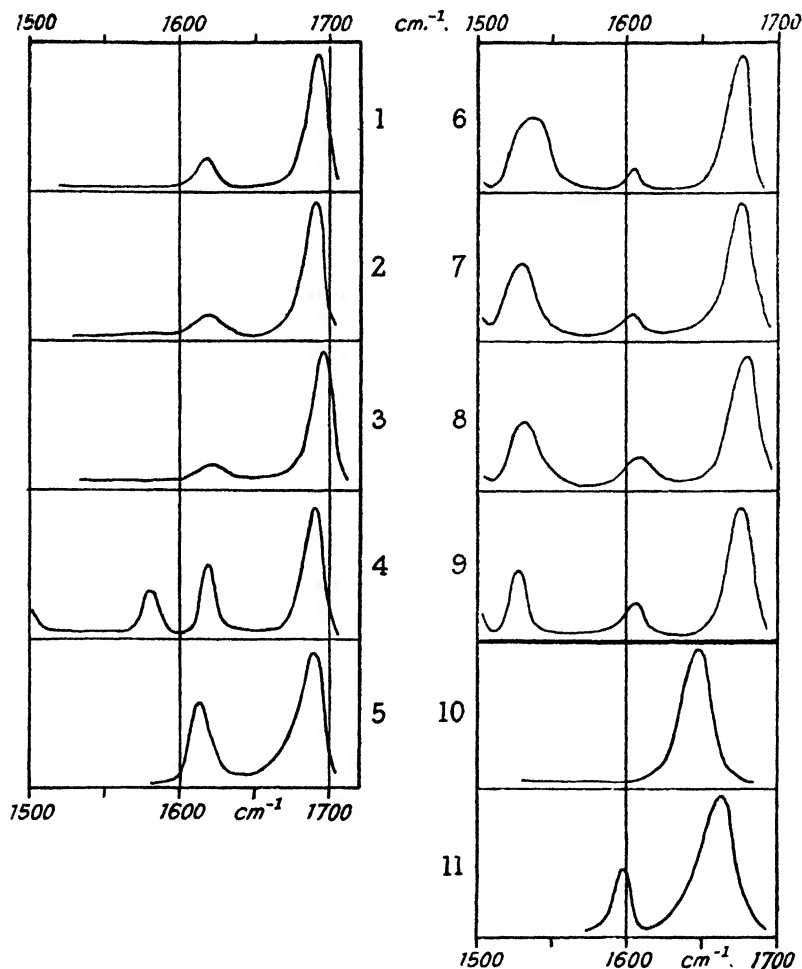
The amide grouping may be expected to have vibrational frequencies corresponding to the stretching of C=O, N-H, C-N, or O-H bonds, and also the associated bending oscillations. These several frequencies will be expected to give rise to absorption bands in the regions $5-7\mu$ and near 3μ . Absorption bands due to less localized vibrations of the molecular skeleton as a whole will for the most part lie at wave-lengths longer than 7μ , and between 7 and 14μ at least are not usually very significant for our present purpose. Results are summarised below of measurements on the spectra of a number of amides in the solid state and in solution, and interpretations are suggested in terms of the possible molecular structure.

EXPERIMENTAL.

Between 7 and 15μ the spectra were measured with a single-beam recording spectrometer using a rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268). Most of the measurements considered here,

however, are for the regions $5-7\ \mu$ and $3\ \mu$, for which a large double-beam recording spectrometer with calcium fluoride prism was used (Sutherland and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 174; Thompson, Whiffen, Richards, and Temple, to be published shortly). This instrument not only has the marked advantage that there is no disturbance in the region $5-7\ \mu$ from the atmospheric water vapour band, but also use is made of the greater dispersion of fluorite compared with rock-salt. Calibration of wave-lengths was obtained with the absorption lines of water, ammonia, carbon dioxide (Oetjen, Kao, and Randall, *Rev. Sci. Instr.*, 1942, **13**, 515), nitrous oxide, and other substances. At about 1700 cm^{-1} the position of bands could be measured to within $\pm 3\text{ cm}^{-1}$, and at 3000 cm^{-1} to within $\pm 8\text{ cm}^{-1}$,

FIG. 1.



Solutions in dioxan.

- | | |
|----------------------------|----------------------------------|
| 1. Butyramide. | 7. Phenylaceto-tert.-butylamide. |
| 2. Hexoamide. | 8. Phenylaceto-tert.-amylamide. |
| 3. Phenylacetamide. | 9. Phenylacetocyclohexylamide. |
| 4. Benzamide. | 10. Acetodiethylamide. |
| 5. Furoamide. | 11. Acetophenylmethylamide. |
| 6. Phenylacetomethylamide. | |

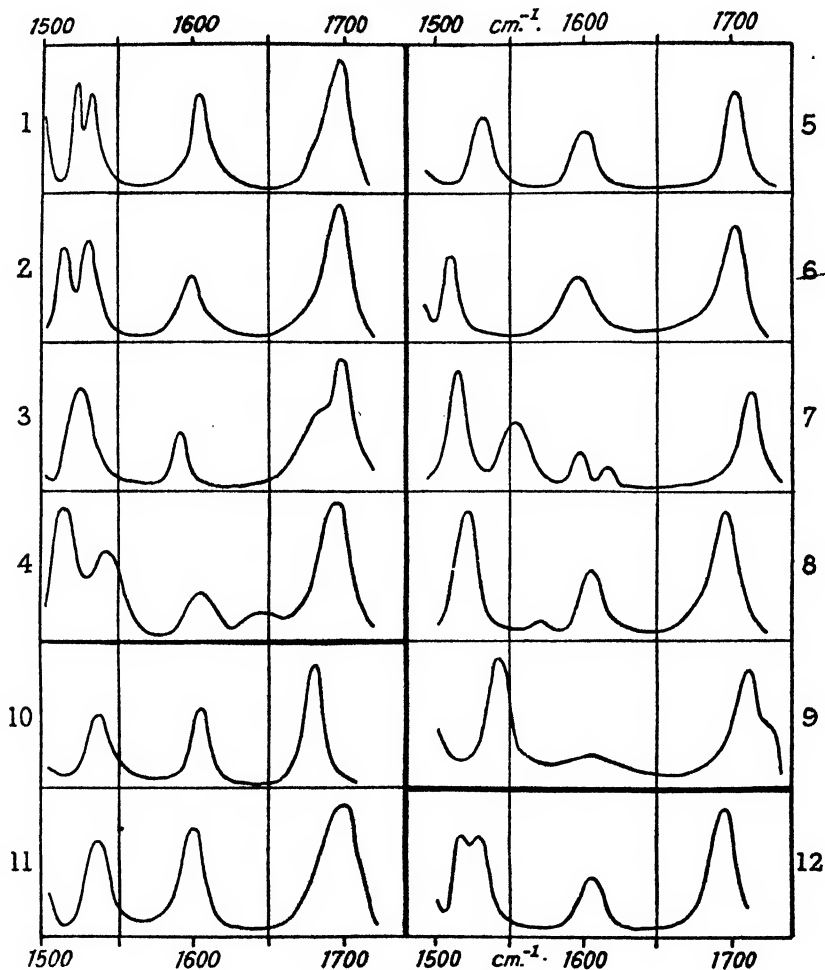
depending upon the breadth of the bands concerned. In many cases where comparisons were being made to discover a general trend, the relative positions of bands of different substances were probably more accurately determined than their absolute values, since several spectra could be measured on the same chart. As indication of the resolving power of the instrument, it was possible when using it as a single-beam spectrometer to resolve clearly lines 2—3 cm^{-1} apart at 1700 cm^{-1} , and about 15 cm^{-1} apart at 3000 cm^{-1} ; with the double-beam arrangement, which necessitated somewhat wider slits, the corresponding figures were about 5 cm^{-1} and 20 cm^{-1} .

Solutions were measured in cells 0.01 and 0.2 cm. in thickness, according to the dilution used. The choice of solvent is limited by the solubilities of these compounds, and by the absorption of the solvent.

Dioxan, chloroform, methyl cyanide, and methanol were normally used, being purified in the standard manner. Amides were measured in the solid state by grinding to a fine paste with medicinal paraffin and pressing between a pair of rock-salt plates. By suitable adjustment of the size of the particles, specimens prepared in this way produce little scattering and a satisfactory spectrum can be obtained with only a few mg. of the solid.

The compounds examined were either prepared in this laboratory or obtained commercially. In all cases they were purified by recrystallisation or other appropriate methods.

FIG. 2.



Solutions in dioxan.

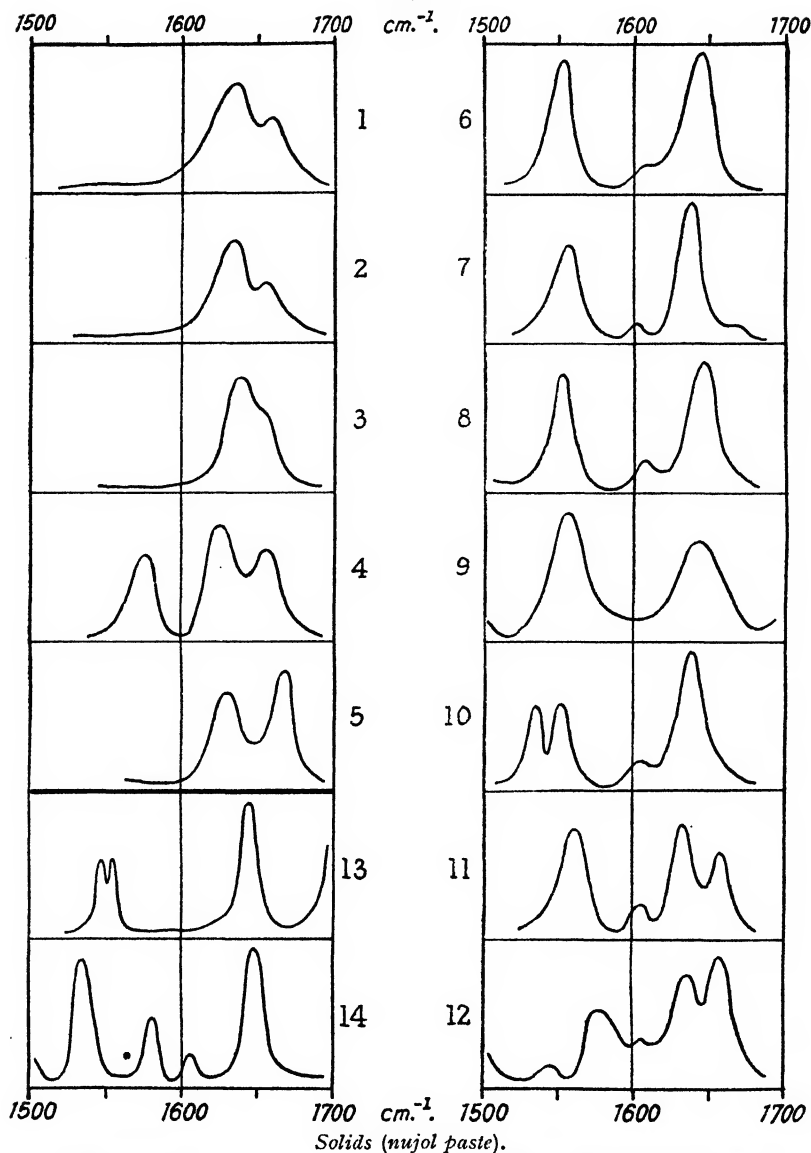
- | | |
|-------------------------------------|---|
| 1. Acetanilide. | 7. <i>p</i> -Nitroacetanilide. |
| 2. Aceto- <i>p</i> -toluidide. | 8. 3-Bromoaceto- <i>p</i> -toluidide. |
| 3. Aceto- <i>o</i> -toluidide. | 9. 3-Bromo-5-nitroaceto- <i>p</i> -toluidide. |
| 4. Aceto- <i>p</i> -methoxyanilide. | 10. Benzanilide. |
| 5. <i>p</i> -Chloroacetanilide. | 11. Phenylacetanilide. |
| 6. <i>p</i> -Bromoacetanilide. | 12. Phenylaceto- <i>p</i> -toluidide. |

Results.—Solutions in dioxan. Fig. 1 shows the spectra (1—5) of five simple unsubstituted amides in dioxan near 6μ . Any effect of this solvent on C=O or C=N groups by association or similar interactions must be negligibly small. Two bands occur in this region, a strong one near 1690 cm^{-1} and a weaker one of somewhat variable intensity at $1615\text{--}1620\text{ cm}^{-1}$. Fig. 1 also shows (6—9) some *N*-alkyl mono-substituted amides, which exhibit two bands at $1675\text{--}1680\text{ cm}^{-1}$ and $1530\text{--}1540\text{ cm}^{-1}$. In these cases the latter band is more marked in intensity than the band of the unsubstituted amides at $1615\text{--}1620$. With the two *NN*-disubstituted amides there is only one band, near 1650 cm^{-1} unless a phenyl group is one of the substituents, in which case the band lies at slightly higher frequencies. All the compounds containing a phenyl group show the well-known sharp, even if weak, bands near 1500 and 1600 cm^{-1} . These results are summarised broadly in Table I. The band at the higher frequencies will be called the A band, and that at the lower frequency the B band.

TABLE I.
Solutions in dioxan.

	Band A.	Band B.
$R \cdot CO \cdot NH_2$	1690	1620
$R \cdot CO \cdot NHalk$	1680	1530
$R \cdot CO \cdot NR_1R_2$	1650	—

FIG. 3.

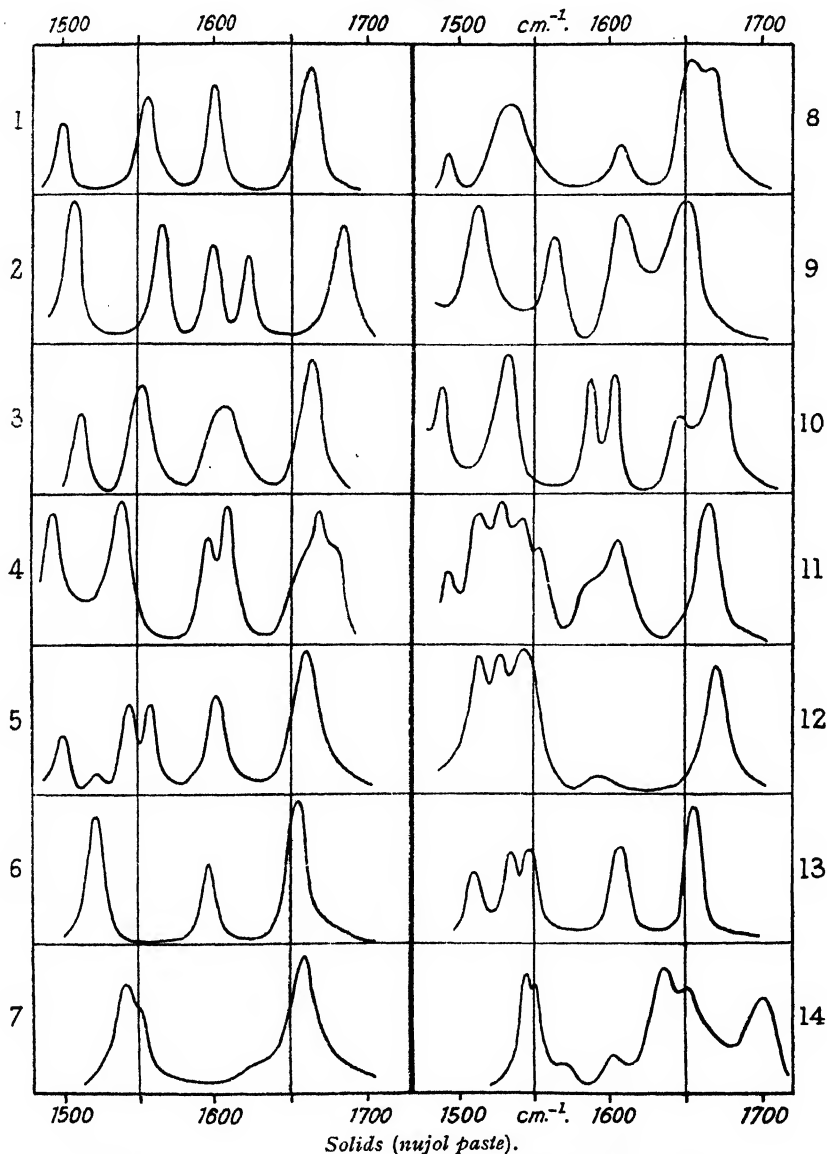


1. Butyramide.
2. Hexoamide.
3. Phenylacetamide.
4. Benzamide.
5. Furoamide.
6. Phenylaceto-tert.-amylamide.
7. Phenylacetocyclohexylamide.
8. Phenylaceto-tert.-butylamide.
9. Methyl phenylacetamidoacetate.
10. Phenylacetobenzylamide.
11. Phenylaceto-n-propylamide.
12. Phenylacetomethylamide.
13. N-Hexoylglycine.
14. Ethyl hippurate.

The results suggest that the band B only appears when there is at least one hydrogen atom in the amide group, and that both the bands A and B are lowered in frequency by substitution of alkyl groups on the nitrogen atom.

Fig. 2 shows the spectra of some derivatives of acetanilide in dioxan. The main feature with these compounds is that the band A lies at about 1700 cm^{-1} , distinctly higher than with the *N*-alkyl-substituted amides. It should be noted that when the group attached to the nitrogen atom is strongly electrophilic, the frequency of this band is further raised, and although such increases of $10\text{--}15\text{ cm}^{-1}$

FIG. 4.



- | | |
|-----------------------------------|---------------------------------------|
| 1. Acetanilide. | 8. Aceto-o-toluidide. |
| 2. p-Nitroacetanilide. | 9. Aceto-p-methoxyanilide. |
| 3. Aceto-p-toluidide. | 10. p-Bromoacetanilide. |
| 4. p-Chloroacetanilide. | 11. 3-Bromoaceto-p-toluidide. |
| 5. Phenylacetanilide. | 12. 3-Bromo-5-nitroaceto-p-toluidide. |
| 6. Phenylaceto-o-toluidide. | 13. Phenylaceto-p-toluidide. |
| 7. Phenylacetamidomethyl cyanide. | 14. Hippuramide. |

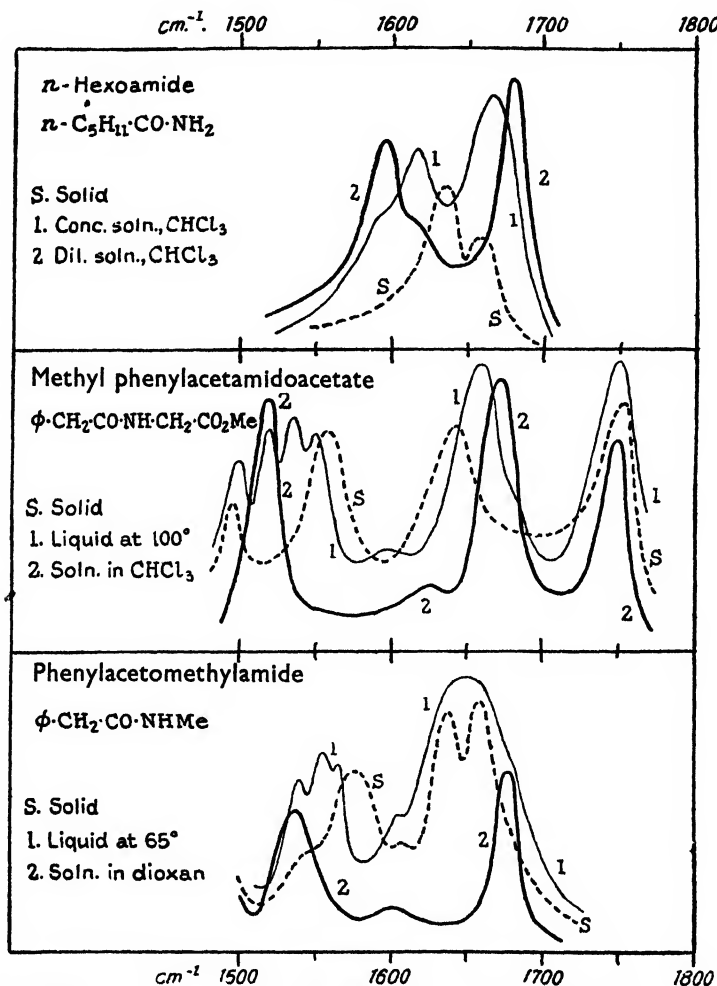
may be regarded as small, they are nevertheless real and regular. Conversely, we should expect electrophobic substituents to lower the frequency, and this seems to occur. As regards the band B of the acetanilides, although there is some interference in the region $1500\text{--}1550\text{ cm}^{-1}$ from bands due to the aromatic ring and other substituent groupings, there seems to be a less definite influence of the *N*-substituents upon its position.

Solutions in other solvents. Many of the amides have also been measured in chloroform and methanol, with particular reference to the position of the band A. The general behaviour found with all amides is that the frequency of this band falls in passing along the series dioxan, chloroform, methanol, and is illustrated by the examples listed in Table II.

TABLE II.

	Frequency (cm. ⁻¹) of band A in :		
	Dioxan.	Chloroform.	Methanol.
Hexoamide	1692	1682	1672
Phenylaceto- <i>tert</i> -amylamide	1682	1668	1657
Aceto- <i>NN</i> -diethylamide	1647	1629	1615 (broad)

FIG. 5.



- (1) *Hexoamide*: s. Solid. 1. Conc. soln. in CHCl_3 . 2. Dil. soln. in CHCl_3 .
 (2) *Methyl phenylacetamidoacetate*: s. Solid. 1. Liquid at 100° . 2. Solution in CHCl_3 .
 (3) *Phenylacetomethylamide*: s. Solid. 1. Liquid at 65° . 2. Solution in dioxan.

Solids. The spectra of a number of solid amides measured as a paste in "Nujol" in the region of 6μ are shown in Fig. 3. In Fig. 4, further examples are given of *N*-monosubstituted amides in which the substituent group has either electron-attracting or electron-repelling character. The simple unsubstituted amides show two fairly close bands in the region 1620 – 1670 cm^{-1} . The *N*-alkylamides show bands at about 1580 and 1640 cm^{-1} , whereas the amides with electrophilic *N*-substituents have the second band—the band A mentioned above—at higher frequencies than 1640 cm^{-1} . The position of the band B is variable, as found with the solutions in dioxan. One solid *NN*-disubstituted amide, namely aceto-*N*-methylanilide, was examined and the position of the band A was hardly affected in

passing from solution in dioxan to the solid state. The above results are summarised broadly in Table III.

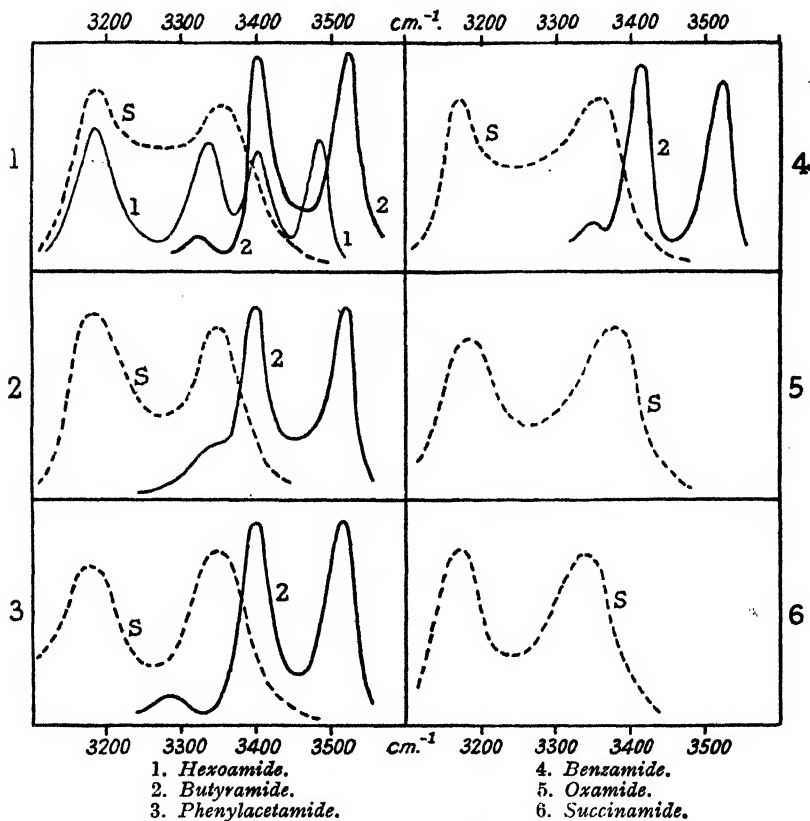
TABLE III.

Solids (R = alkyl, R_e = electrophilic group).

Approximate position (cm.⁻¹) of bands:

	A.	B.
R'-CO-NH ₂	1655	1630
R'-CO-NHR	1640	1560
R'-CO-NHR _e	1660—1680	1530—1570

FIG. 6.



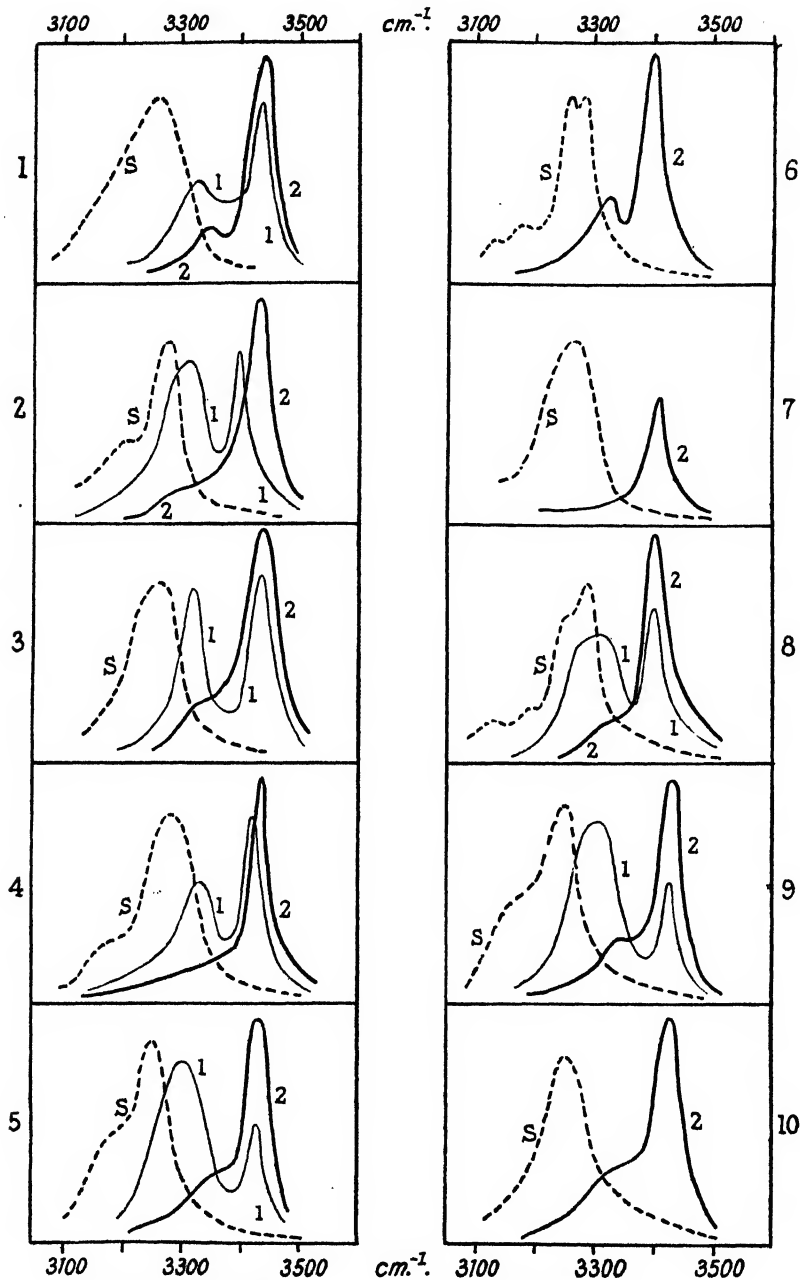
s. Solid. 1. Conc. soln. in CHCl₃. 2. Dil. soln. in CHCl₃.

It can be seen that in the solid state the unsubstituted amides show the A band at about 1655 cm.⁻¹, and the *N*-alkyl-substituted amides at about 1640 cm.⁻¹, in both cases a noticeable decrease from the values found (Table I) for the solutions in dioxan. With the *NN*-disubstituted amides, either liquid or solid, there is little change in the frequency of this band on passing from the liquid or solid to the solution, although the band may broaden. With the solid *N*-alkylamides a fairly strong band appears at about 1560 cm.⁻¹, corresponding to that at 1530 cm.⁻¹ with solutions in dioxan.

The increase in frequency of the A band of the solids when the *N*-substituent is electrophilic is parallel to the change found with the solutions. It may also be noted that when this band is raised in frequency by the electrophilic substituent, the band normally at 1560 cm.⁻¹ is generally lowered. Finally, the relative intensity of the bands A and B appears to alter with the change of state, the latter usually becoming stronger with the solid.

Gradual Transitions from Solid or Liquid to Dilute Solution.—Several examples have been examined of the changes associated with the transition from the solid or liquid amide to a very dilute solution, through intermediate concentrations of the solute. Some of the results are shown in Fig. 5 for *n*-hexoamide, phenylacetomethylamide, and methyl phenylacetamidoacetate in chloroform. Some of bands shown are connected with groups with which we are not immediately concerned; for example, that at 1750 cm.⁻¹ due to the carbonyl group of the ester. The main point to notice is that in every case the passage from the solid (or liquid) to the dilute solution brings about an increase in the frequency of the band A and a simultaneous decrease in the frequency of the band B. Thus with hexoamide, the

FIG. 7.



1. Phenylacetomethylamide.
2. Phenylaceto-*tert*-butylamide.
3. Phenylaceto-*n*-propylamide.
4. Phenylaceto-*tert*-amylamide.
5. Phenylacetocyclohexylamide.

6. Phenylacetanilide.
7. Phenylaceto-*o*-toluidide.
8. Phenylaceto-*p*-toluidide.
9. Phenylacetamidomethyl cyanide.
10. Methyl phenylacetamidoacetate.

s. Solid. 1. Conc. soln. in CHCl_3 . 2. Dil. soln. in CHCl_3 .

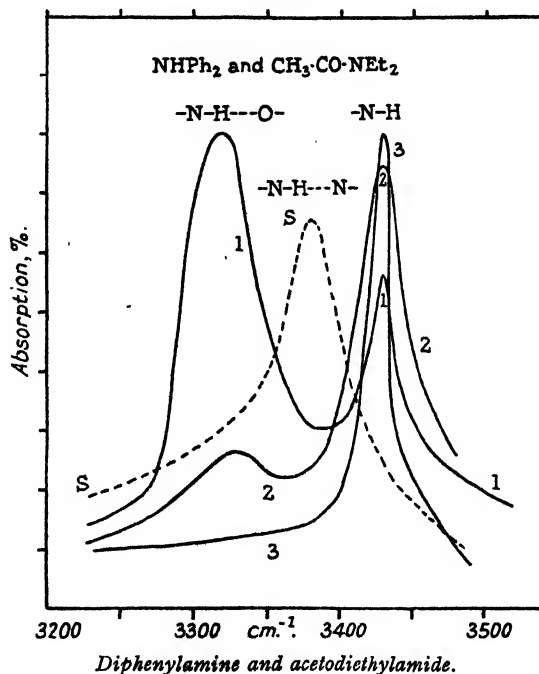
solid has the bands at 1655 and 1635 cm^{-1} , in concentrated solution they lie at 1668 and 1615 cm^{-1} , and in dilute solution at 1680 and 1595 cm^{-1} . With methyl phenylacetamidoacetate the solid has bands at 1642 and 1557 cm^{-1} , the liquid (at 100°) at 1660 and 1535 cm^{-1} , and the solution in chloroform at 1672 and 1517 cm^{-1} . (The band at about 1750 is due to the carbonyl link in the ester group.)

The region of 3 μ . The spectra of many unsubstituted and *N*-substituted amides have been measured between 3000 and 3600 cm^{-1} , as solids and also as solutions in chloroform. The curves are shown in Figs. 6 and 7. With substances containing phenyl radicals, there is usually a band near 3070 cm^{-1} connected with a vibration of the aromatic C-H linkages, but this is not significant for our present purpose. Dilute solutions of the unsubstituted amides appear to have two sharp bands at about 3400 and 3520 cm^{-1} , which give place in the solids to two others at about 3180 and 3350 cm^{-1} . In concentrated solutions all four bands may appear simultaneously.

In dilute solutions, the *N*-monosubstituted amides have one sharp band at about 3430 cm^{-1} which gives place in the solid to a broader band at about 3270 cm^{-1} . In concentrated solutions the latter band seems to appear at frequencies rather higher than 3270 cm^{-1} , and can be found concurrently with the sharp band near 3430 cm^{-1} .

In connexion with the possible interpretation of these bands and shifts, we have examined the spectra of diphenylamine in dilute solution in carbon tetrachloride and as a solid, and also of solutions of diphenylamine to which acetodiethylamide had been added. This experiment is a variant on that

FIG. 8.



- s. Solid diphenylamine.
1. 2 G. diphenylamine + 1 c.c. acetodiethylamide: 25 c.c. CCl_4 , 0.1 mm. thick.
 2. 2 G. diphenylamine + 1 c.c. acetodiethylamide: 500 c.c. CCl_4 , 2.0 mm. thick.
 3. 2 G. diphenylamine + 1 c.c. acetodiethylamide: 5000 c.c. CCl_4 , 2 cm. thick.

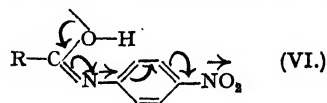
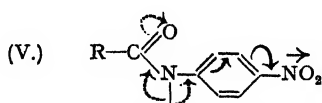
previously described by Buswell, Downing, and Rodebush (*loc. cit.*). The results are depicted in Fig. 8. It can be seen that the dilute solution of diphenylamine has the N-H stretching vibration band at 3430 cm^{-1} , but in the solid state this is replaced by the broader association band at 3380 cm^{-1} . Similar N-H---N association has been recorded with ethyleneimine (Thompson and Harris, *J.*, 1944, 301). When the acetodiethylamide is added to the solution of diphenylamine, the band at 3430 cm^{-1} is diminished in intensity and a new band appears at 3320 cm^{-1} . This change corresponds to the formation of N-H---O bridges. As the mixture of diphenylamine and acetodiethylamide is diluted, the association band at 3320 cm^{-1} is much diminished whilst the normal N-H frequency at 3430 cm^{-1} is strengthened. This phenomenon is markedly parallel to that seen in Fig. 7 for the *N*-substituted amides.

DISCUSSION.

The results described above show that the vibration frequencies exhibited by amides are much affected by the change of state from solid to solution. It will be convenient first to consider the spectra of solutions before discussing the shifts which occur on passing to the solids.

As already stated, a simple *N*-monosubstituted amide could exist as either the ketonic (I) or the enolic (II) form, each of these being capable of hybridisation with its corresponding dipolar structure, (III) and (IV), respectively. The band A of *NN*-disubstituted amides which occurs at about 1650 cm^{-1} must be attributed to the stretching vibration of the C=O bond, since

no enolisation of the conventional type can occur. The lower value as compared with that in ketones—about 1710 cm^{-1} —will result from the resonance with the ionic form. In the case of the simple or *N*-monosubstituted amides the band A could be interpreted in the same way. In this case, however, enolisation would lead to some form of $\text{C}=\text{N}$ link, and it is well known from the Raman spectra of ketoximes that this can give rise to a band in the region $1650\text{--}1660\text{ cm}^{-1}$ (Hibben, "The Raman Effect," p. 280). Now the above measurements with the amides having a strongly electrophilic *N*-substituent provide an argument against this correlation of the band A with the vibration of a $\text{C}=\text{N}$ bond, as follows. If the amide has the ketonic form, the presence of strongly electrophilic groups on the nitrogen atom should cause the dipolar form (III) to be less stable relative to the non-polar form (I). Alternatively, the electron-attracting groups can be regarded as opposing the conjugation from the nitrogen atom to the carbonyl group, as in



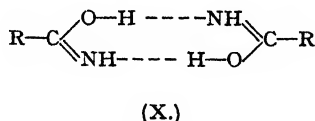
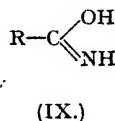
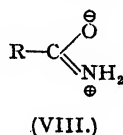
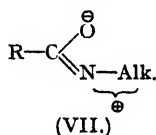
(V). In these circumstances the carbonyl group will be expected to have greater double-bond character, and a rather higher stretching-vibration frequency, which is in fact found. If the molecule existed in the enolic form, however, the converse would apply. An electrophilic substituent on the nitrogen atom would then favour the dipolar form, shown by (VI), and the double-bond character of the $\text{C}=\text{N}$ bond would be lowered.

It therefore seems satisfactory to attribute the band A in the amides as a whole to the stretching vibration of the essentially ketonic carbonyl group. In connexion with these arguments it is interesting to consider the effect of *N*-alkyl substituents upon the frequency of the band A. The results of Table I and Fig. 1 suggest that these groups have an opposite effect to those groups which are known to be electron-attracting. Now, alkyl groups are known to be readily polarisable (Ingold, *Chem. Reviews*, 1934, 15, 238), that is, they can provide or accept electrons according to the particular group to which they are attached. This is well illustrated by the values for the dipole moments of some simple compounds quoted by Watson ("Modern Theories of Organic Chemistry," 2nd edition, p. 93), and listed in Table IV. It is possible,

TABLE IV.
Dipole moments of compounds RX.

R/X =	Cl.	Br.	I.	CN.	NO ₂ .	OH.
H	1.03	0.78	0.38	2.93	—	1.84
CH ₃	1.87	1.80	1.64	3.94	3.54	1.69
C ₂ H ₅	2.05	2.01	1.87	4.04	3.68	1.69

therefore, that in the alkyl-substituted amides the fractional positive charge on the nitrogen atom is shared by the alkyl group. In other words, the energy of the charge separation in (VII)



is lower than in (VIII). In that case, the relative contribution of (VII) to the hybrid will be greater than that of (VIII), so that the carbonyl group will have less double-bond character and a lower vibration frequency in the alkyl derivatives.

The interpretation of the band B found between 1520 and 1630 cm^{-1} with the unsubstituted and *N*-monosubstituted amides is more difficult. It might be explained in four ways, namely, (i) as the stretching vibration of the C-N link in a ketonic form, if this bond has acquired considerable double-bond character due to resonance with the dipolar form; (ii) as the stretching vibration of the $\text{C}=\text{N}$ link in an enolic form, reduced in frequency by resonance with its dipolar structure; (iii) as a bending frequency of the N-H link; or (iv) as an overtone or combination band. As already explained, the band is not observed with disubstituted amides where there will certainly be contributions from the dipolar form. Also, the degree of double-bond character required to produce such a high frequency seems much greater than is plausible from the molecular bond lengths found in some solid amides such as acetamide (Senti and Harker, *loc. cit.*). These arguments make the first interpretation improbable.

The assignment of the band B to the $C=N$ link of an enolic form would imply the simultaneous existence of both ketonic and enolic forms both in solution and in the solid state. The X -ray measurements have shown, however, that in the solid state only the ketonic form is present. Further, in no case is the shift produced by the substitution of an electron-attracting group by an alkyl group consistent with this interpretation. Also, the band B increases in frequency on passing from the solution to the solid. This is contrary to what would be expected if this change were accompanied by the formation of bridged links in passing from (IX) to (X).

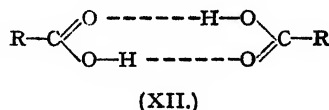
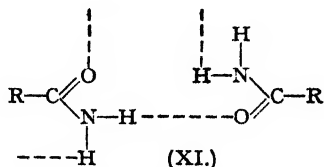
Finally, if an amide were to exist as a mixture of the ketonic and the enolic form, samples from different sources and recrystallised from different solvents would be expected to show different proportions of the two forms. In no case have such variations been detected.

The possibility that the band B is due to an overtone cannot be ruled out, but it is improbable. The band varies in intensity in different compounds, but with the N -monosubstituted derivatives it is usually stronger than might be expected for anything but a fundamental. Experiments with deuterated compounds might help to settle this question.

The third possibility seems to us the most reasonable. It explains the absence of the band in the disubstituted amides, and the shift of the band B in passing from the solid to solution—namely, a decrease in frequency—agrees with that expected of a bending mode of the $N-H$ link if the latter takes part in hydrogen bridges in the solid state. The difference between the band B in unsubstituted amides on the one hand, and N -monosubstituted amides on the other, can be explained by interaction between the two $N-H$ bonds in the former case. Hence, it seems that in dilute solution in dioxan, the amides exist predominantly in the ketonic form.

The results of Table II illustrate the effect of solvent on the stretching frequency of the carbonyl group. This may be due to two causes, namely, the difference in dielectric constant of the medium, or the effect of hydrogen bonding from the solvent to the carbonyl group of the amide. The energy of the charge separation in (VII) or (VIII) might be lowered by an increase in the dielectric constant of the medium, and the stretching frequency of the carbonyl group would then be expected to lie at lower values than in a medium of low dielectric constant. In methyl cyanide, however ($\epsilon = 37.5$), the frequency of the carbonyl group is substantially the same as in dioxan ($\epsilon = 2.2$), so this influence of dielectric constant cannot be very significant. On the other hand, solvation by hydrogen bonding to a carbonyl group lowers the frequency of the latter. With acetone in carbon tetrachloride solution, it lies at 1710 cm^{-1} , but in methyl alcohol at 1701 cm^{-1} . It is therefore possible that the changes shown in Table II are caused by a change in hydrogen bonding from the solvent to the carbonyl group.

In the solid state, the stretching frequency of the carbonyl group in an unsubstituted or N -monosubstituted amide lies at a much lower value than in dilute solution in dioxan, whilst the band B lies at higher values. Our own measurements, and those of Gordy (*J. Chem. Physics*, 1939, 7, 163) show, as just outlined, that the frequency of the carbonyl group is reduced by hydrogen bonding. Since the X -ray measurements indicate that acetamide exists in a



polymeric form (XI), it is evident that the bonding will lower the frequency of the carbonyl group. Moreover, in such polymers, the strength of the hydrogen bridges will be increased by the presence of a greater positive charge on the nitrogen atom, or a greater negative charge on the oxygen atom, and therefore by an increase in the contribution of the dipolar structure to the hybrid. It follows that in the associated form of the amides the carbonyl link will have a smaller double-bond character than in the unassociated form, and hence a lower frequency of vibration. The NN -disubstituted amides, which cannot undergo such association, show no such shifts of the frequency with change of state.

That this association has a powerful effect on the stretching vibration frequency of the carbonyl group is further borne out by our measurements on acetic acid and phenylacetic acid in the liquid and in the solid state, where the substances are known to exist as dimers of the type (XII). With liquid acetic acid the band lies at 1712 cm^{-1} , and with solid phenylacetic acid there is a double band at 1704 — 1692 cm^{-1} . A dilute solution of acetic acid in dioxan, however, shows bands at 1730 and 1753 cm^{-1} , which may correspond to the dimeric and the monomeric

form. Herman and Hofstadter (*J. Chem. Physics*, 1939, 7, 460) have similarly shown that in the vapour state the frequencies of the carbonyl group in dimeric and monomeric aliphatic acids lie at about 1740 and 1770 cm^{-1} , so the shift is about 30 cm^{-1} . In dioxan, phenylacetic acid shows one sharp band at 1735 cm^{-1} , and the shift in passing from the dimer to the monomer is therefore closely parallel to that found with amides in passing from solutions in dioxan to the solid state.

If this interpretation of the shift is correct, we might expect that in concentrated solutions of the amides, the co-existence of both unassociated and associated forms might give rise to two frequencies of the carbonyl group, and there is some evidence to support this. The curves of Fig. 5 show that the band due to the carbonyl group is broad with concentrated solutions of hexoamide and phenylaceto-*tert*.-butylamide, and there are signs of a double band. Dilute solutions of hexoamide in chloroform show three bands at 1595 (strong), 1615 (weak), and 1678 (strong and sharp), whereas with concentrated solutions the bands are at 1595 (weak), 1615 (strong), and 1668 (strong and broad). This suggests that in concentrated solutions the dimers giving rise to 1615, 1668 predominate, whilst in dilute solutions the monomer (1595, 1678) is in excess. Two amides were examined as liquids at temperatures above their melting point, and the bands A and B were displaced to positions intermediate between those found for the solids and for the solutions, and were also broad suggesting the presence of more than one species.

To sum up, therefore, the bands in the region 5–7 μ suggest that amides have the ketonic structure, resonating with its corresponding dipolar form. In dilute solution in dioxan and chloroform the amides appear to be monomeric, but in more concentrated solutions in chloroform, and in the liquid state, association occurs. In the solid state this association is complete.

In the region of 3 μ we should expect to find absorption bands due to the stretching vibration of N–H links, and of O–H links if present. In dilute solutions, the unsubstituted amides show sharp bands at about 3400 cm^{-1} and 3520 cm^{-1} , which might at once be correlated with the symmetrical and antisymmetrical vibrations of the NH_2 group in an unassociated form. On the other hand, the band at 3520 cm^{-1} might be assigned to the O–H link of an enolic form. However, the frequency due to the unassociated hydroxyl link in a large number of alcohols and phenols lies between 3610 and 3680 cm^{-1} , and with fatty acids at about 3550 cm^{-1} . We might therefore expect the unassociated hydroxyl band in an enolized amide to lie at about 3600 cm^{-1} . Only in the case of trichloroacetic acid (Buswell, Rodebush, and Roy, *J. Amer. Chem. Soc.*, 1938, 60, 2239) does this band lie at a frequency as low as 3520 cm^{-1} , and in this case the O–H link must certainly be weaker than in the amide. Hence it is unlikely that the amide band at 3520 cm^{-1} could be due to the hydroxyl group, and the explanation given at the start is to be preferred.

In very dilute solution, the *N*-monosubstituted amides show one band at 3420–3440 cm^{-1} . This low value cannot possibly be due to an enolic O–H group, and lies as expected between the two frequencies of the unsubstituted amides. *NN*-Disubstituted amides show no absorption in this region.

In the solid state, the unsubstituted amides have strong bands at about 3180 and 3350 cm^{-1} , which are plausibly interpreted as being due to two bonded N–H groups of a polymeric complex such as was indicated above. In the concentrated solutions, illustrated for hexoamide in Fig. 6, both the association bands at 3180, 3350 cm^{-1} , and the unassociated N–H bands at 3400, 3520 cm^{-1} appear simultaneously.

N-Monosubstituted amides have one band only in the solid state, at 3270 cm^{-1} , which again corresponds to a bonded N–H group. Here too, in concentrated solutions, both the association band and the "normal" band at 3430 cm^{-1} are simultaneously present. In these cases the association band appears to shift gradually towards higher frequencies and has a diminishing intensity as the dilution is increased, which would imply some gradual weakening of the bonding strength.

This interpretation of the bands of *N*-monosubstituted amides near 3 μ is supported by the measurements already described with diphenylamine and acetodiethylamide. These showed that the unbonded N–H link in diphenylamine has a frequency of 3430 cm^{-1} , and the strongly bonded N–H --- O group has a frequency of 3320 cm^{-1} . These values fall exactly into line with those for the unsubstituted amides.

It seems, therefore, that the spectroscopic data in both the regions, 3 μ and 6 μ , indicate the existence of the amides in the ketonic form, which associates through N–H --- O bonds in concentrated solutions, in the liquids and in the solids. This preliminary survey will be useful in our later consideration of the more complex amides, amino-acids, and peptides.

We thank the Government Grant Committee of the Royal Society for a grant in aid of equipment, and the Department of Scientific and Industrial Research for a Maintenance Grant to one of us. We are also pleased to record appreciation of some valuable discussions which one of us had with workers at the University of Michigan, and at the Shell Development Company, Emeryville, during 1945, on the above and related problems.

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[Received, November 6th, 1946.]

238. Vibrational Spectra of Phenolic Derivatives and Phenolic Resins.

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The vibrational spectra of some substituted phenols and related compounds, and of some resins formed from phenols and aldehydes, have been examined. The possibility of formulating correlation rules for use in determining structural features of the resins has been explored. From the bands observed in the region $700\text{--}900\text{ cm}^{-1}$ it may be possible to infer the type of substitution around the aromatic nuclei in these complex molecules. The absorption of hydroxyl groups in the region $3200\text{--}3650\text{ cm}^{-1}$ reveals differences in the types of hydrogen bonds in the different compounds and suggests that differences between resins made from the same materials may be related to this particular structural feature. Some of the compounds have been measured both as solids and as liquids and spectral differences in the two states of aggregation have been found.

INFRA-RED spectroscopy has recently been used in examining compounds of high molecular weight, and some results have emerged which might not have been derivable by other methods (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; *Proc. Roy. Soc.*, 1945, **184**, A, 3, 21). Among other classes of compound we have studied the resins formed by condensation of phenols with aldehydes, the aim being to discover more about the mechanism of condensation and the nature of cross linkage in these structures. Whilst some empirical spectral differences between different resins were of immediate practical interest, it became clear that the only satisfactory way of understanding the spectra would be to collect results for a large number of structurally related simpler molecules from which closer correlations with molecular structure could be made. In the course of this investigation some interesting facts have emerged about the association which occurs with these hydroxylic compounds, and the nature of the hydrogen bridges which arise. Some of the results are given in the present paper.

EXPERIMENTAL.

The spectra between 6 and $15\text{ }\mu$ were measured on a single-beam recording spectrometer with rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268). The measured frequencies were accurate to $\pm 5\text{ cm}^{-1}$ at $7\text{ }\mu$, and to $\pm 2\text{ cm}^{-1}$ at $15\text{ }\mu$. Between 2.5 and $6\text{ }\mu$ a double-beam recording spectrometer was used (see preceding paper). With this spectrometer, the frequencies of bands near $7\text{ }\mu$ could be determined to $\pm 3\text{ cm}^{-1}$, and at $3\text{ }\mu$ to $\pm 8\text{ cm}^{-1}$ depending upon their breadth. At $3\text{ }\mu$ it was possible to resolve bands 20 cm^{-1} apart, although when the instrument was used as a single-beam spectrometer rather better resolution was possible.

Solutions in carbon disulphide were measured in rock-salt cells about 0.1 mm. thick. Solutions in carbon tetrachloride were studied at $3\text{ }\mu$ in rock-salt cells of thickness 2 mm. , 3.5 cm. , and 7.8 cm. , according to the dilution being used. Solids were examined either by melting them and allowing them to crystallise between a pair of rock-salt plates, or by the method of a paste in paraffin used in the preceding paper. Measurements at higher temperatures were made with an electrically heated cell (Richards and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 183).

Many of the phenolic derivatives were kindly supplied by Messrs. Bakelite Ltd. or by the Chemical Laboratory, Teddington. Others were commercial samples purified in this laboratory in the appropriate manner. The resins were supplied by Messrs. Bakelite Ltd. and by other firms.

RESULTS AND DISCUSSION.

Figs. 1 and 2 show the spectra between 700 and 1500 cm^{-1} ($14\text{--}6.5\text{ }\mu$) of some phenols, aromatic alcohols, and other compounds likely to have a bearing on the structure of the resins themselves. Each of the spectra is complex, and few correlations are immediately obvious. All the compounds show one or more intense bands in the region $700\text{--}870\text{ cm}^{-1}$, and these are of particular interest since it has previously been found that substituted benzenes have more or less characteristic frequencies in this range, according to the number and position of the substituents and in great measure independent of their exact nature (Thompson and Torkington, *loc. cit.*; Whiffen and Thompson, *loc. cit.*). The normal vibration of benzene in which the group of six carbon atoms moves in a rigid plane perpendicularly to the plane containing the six

hydrogen atoms has a frequency of 671 cm^{-1} . Previous results have shown that when the substituent is attached to the ring, this type of vibration, which is essentially a deformation of the remaining C-H bonds, is displaced to 740–760 cm^{-1} . With disubstituted benzenes, the corresponding vibration has a frequency which depends on the relative position of the substituents; with *o*-derivatives it usually lies at 740–760 cm^{-1} , with *m*-compounds at 770–790 cm^{-1} , and with *p*-compounds at 810–830 cm^{-1} . With tri- and tetra-substituted benzenes the corresponding deformations of the residual C-H bonds also appear to have fairly definite frequencies. The earlier work suggested for the 1:2:3-derivatives a band at 760–770 cm^{-1} , for 1:2:4-compounds a band at 800–820 cm^{-1} , and for 1:3:5-compounds at 825–860 cm^{-1} . With the 1:2:3:5- or 1:2:4:5-compounds the band lies in the region 850–880 cm^{-1} .

The present results appear in most cases to conform with these correlations. Thus, mono-substituted benzenes include:

Benzyl alcohol	745 cm^{-1}	Diphenyl ether	752 cm^{-1}
β -Phenylethyl alcohol	748 „	Diphenylmethane	735 „
Dibenzyl ether	746 „		

Typical disubstituted benzenes include the following:

<i>ortho</i> -		<i>para</i> -	
Fluorene	741 cm^{-1}	4:4'-Dihydroxydiphenylmethane ...	816 cm^{-1}
Diphenylene oxide	750 „	2:4'-Dihydroxydiphenylmethane ...	810 „
2:4'-Dihydroxydiphenylmethane	752 „	4:4'-Dihydroxydiphenylmethane ...	827 „
2:2'-Dihydroxydiphenylmethane	754 „		

Some compounds show simultaneously the mono- and di-substituted type, such as

	Mono.	<i>o</i> -Di.	<i>p</i> -Di.
<i>p</i> -Hydroxydiphenyl	755	—	830
<i>o</i> - „ „	730	754	—

Polysubstituted benzenes include the following:

3-Hydroxymethyl- <i>p</i> -cresol (1:2:4)	815 cm^{-1}
3:5-Bishydroxymethyl- <i>p</i> -cresol (1:2:3:5)	864 „
5-Hydroxymethyl- <i>o</i> -4-xyleneol (1:2:4:5) ...	856 „

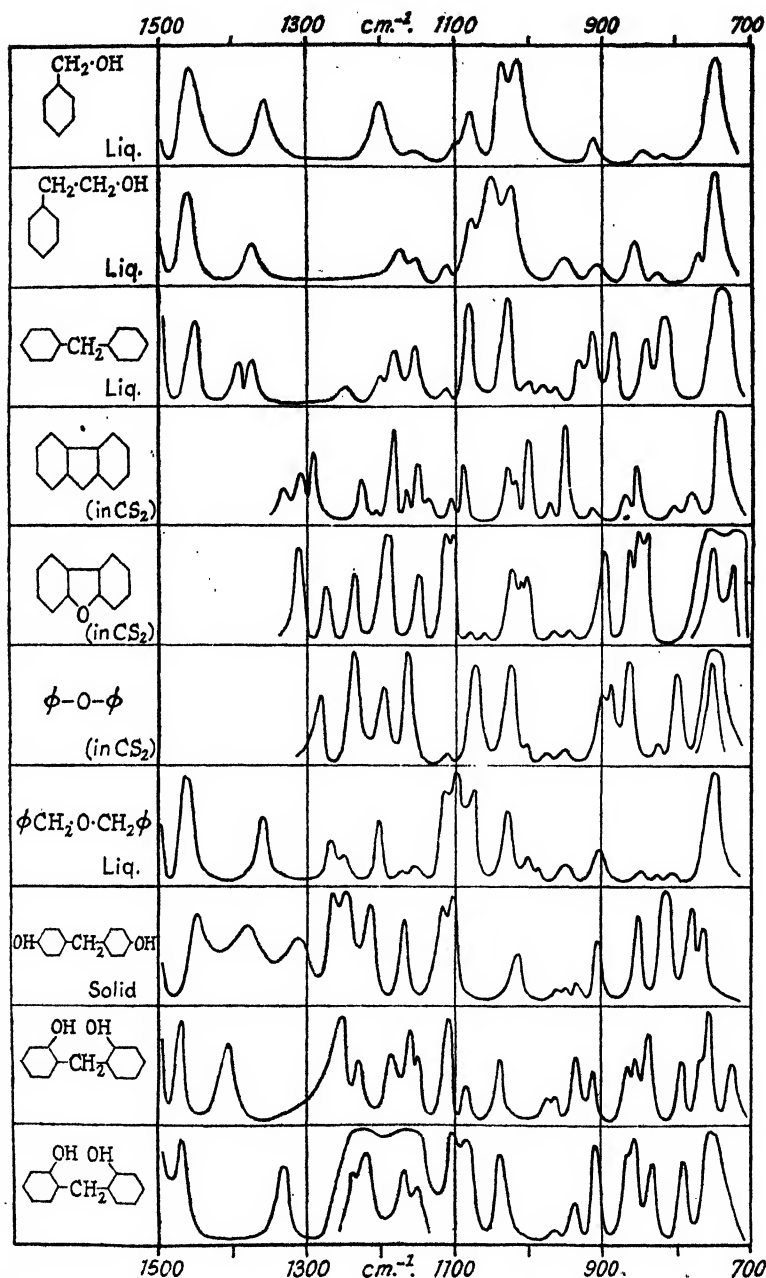
It is clear, therefore, that these correlation rules are fairly widely applicable, although it is obvious that since there are small variations within a given class there may in some cases be ambiguity and the rules must be used with caution. Also, whilst the correlations do not seem to be seriously affected by a change of state of the substance being measured, this possibility must not be excluded.

It is impossible to assign the bands between 1000 and 1500 cm^{-1} to particular normal modes, although this region will include vibrations of the groups C-O-C, C-O-H, CH₂, and CH₃, as well as of the skeleton of the aromatic rings. It is, however, apparent that in these cases the exact position of a particular band depends upon the environment of the group within the molecule. It is hoped shortly to explore this region in greater detail under higher resolving power.

Some of the substances given in Figs. 1 and 2 were measured in the solid and in the liquid state, or in solution. In some cases there are striking changes of spectrum with change of state, which have been noted already in other connexions (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, 41, 260; Thompson, *Nature*, 1946, 158, 234). In order to eliminate the possibility of decomposition on melting, the procedure was to measure the spectrum of the liquid first, then to allow it to crystallise between the rock-salt plates, and then to measure the solid film again. The spectrum of this solid film was also compared with that obtained by measuring the paste formed by grinding with paraffin. The spectrum of the monoalcohol of *m*-4-xyleneol was measured at 100° and 250°, but showed no appreciable change, and other liquids showed no change of spectrum with temperature. It seems certain, therefore, that the marked changes of spectrum at the melting point must be connected with fresh influences which come into play in the arrangement of the molecules in the solid. The spectra of the solids usually show sharper bands than those of the liquids, and new bands appear which are absent with the latter. This whole problem is being examined more systematically, and a detailed consideration of the physical principles involved will therefore be deferred.

In Fig. 3 (Nos. 1, 2, 3, 4, 5) the spectra around 3 μ are shown of some simple *p*-substituted phenols in the solid state, and of dilute solutions in carbon tetrachloride. In the dilute solutions the normal sharp band of the hydroxyl group occurs at 3615 cm^{-1} . With the solids, this band

FIG. 1.

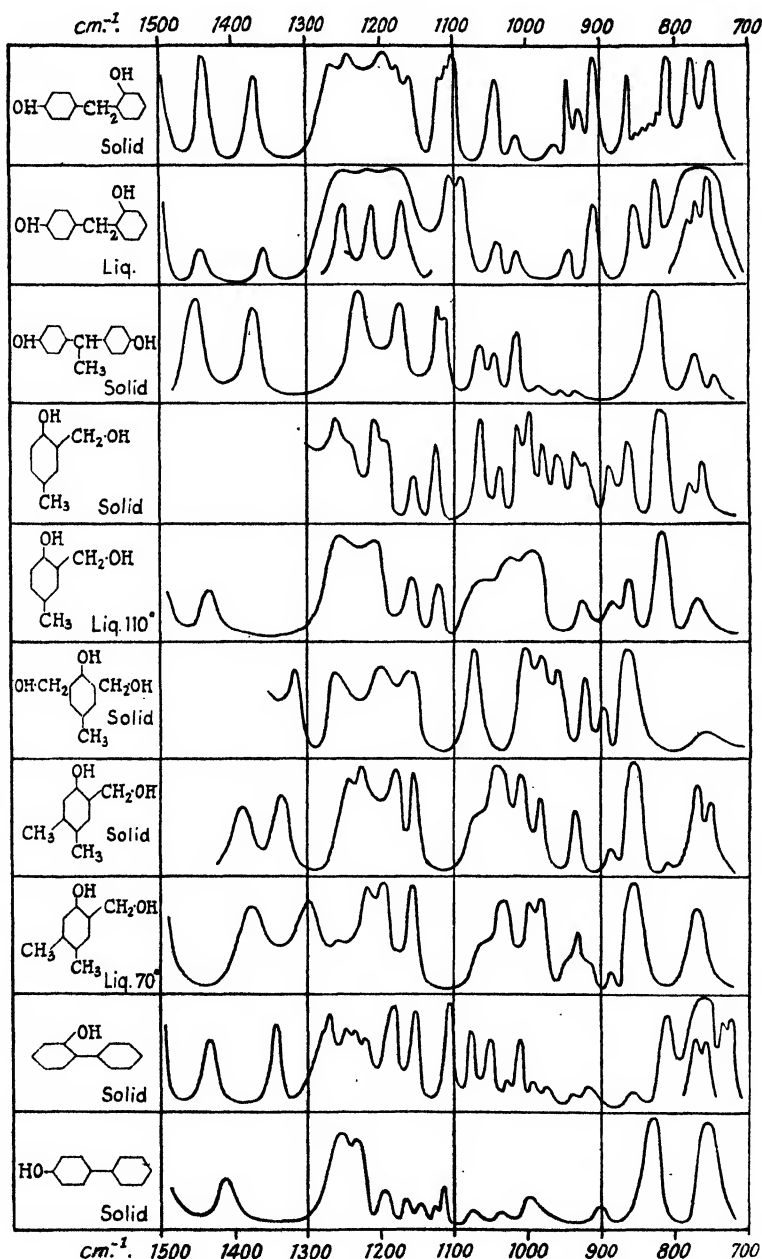


1. Benzyl alcohol (liquid).
2. β -Phenylethyl alcohol (liquid).
3. Diphenylmethane (liquid).
4. Fluorene (in carbon disulphide).
5. Diphenylene oxide (in carbon disulphide).
6. Diphenyl ether (in carbon disulphide).
7. Dibenzyl ether (liquid).
8. 4:4'-Dihydroxydiphenylmethane (solid).
9. 2:2'-Dihydroxydiphenylmethane (solid).
10. 2:2'-Dihydroxydiphenylmethane (liquid).

is replaced by a broader band with centre at $3200\text{--}3250\text{ cm}^{-1}$, corresponding to the "bonded" hydroxyl group. With concentrated solutions, both the normal and the "association" band may appear simultaneously. These relationships correspond to those already examined by Fox and Martin, and others.

When there is a substituent in the *o*-position to the hydroxyl group (Fig. 4, Nos. 1, 2, 3, 4) the position of the "normal" hydroxyl group band in dilute solution is again at about 3615 cm^{-1} , but the association band with the solids lies at rather higher frequencies than in the above cases of the simple *p*-substituted phenols. This implies that the screening of the hydroxyl

FIG. 2.



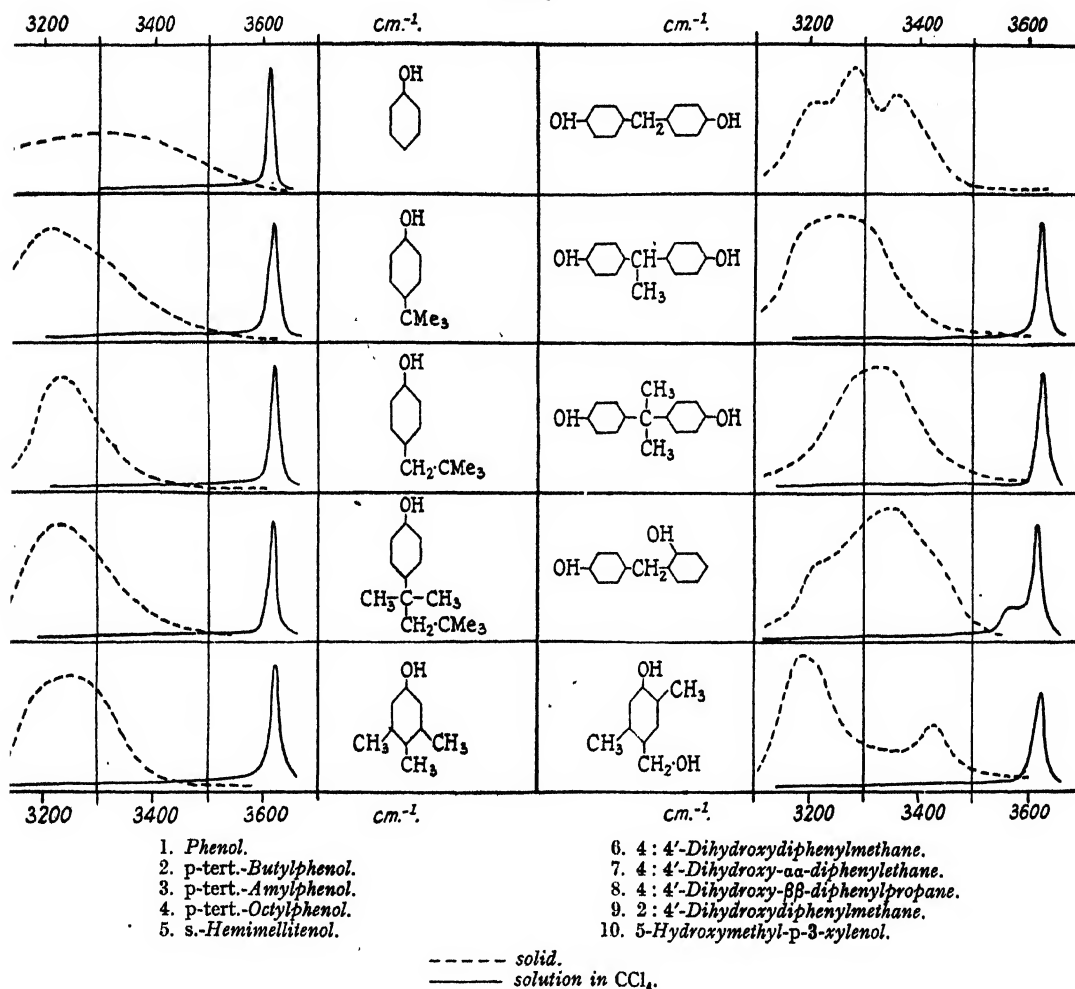
1. 2 : 4'-Dihydroxydiphenylmethane (solid).
2. 2 : 4'-Dihydroxydiphenylmethane (liquid).
3. 4 : 4'-Dihydroxy- α -diphenylethane (solid).
4. 3-Hydroxymethyl-*p*-cresol (solid).
5. 3-Hydroxymethyl-*p*-cresol (liquid).

6. 3 : 5-Bishydroxymethyl-*p*-cresol (solid).
7. 5-Hydroxymethyl-*o*-4-xyleneol (solid).
8. 5-Hydroxymethyl-*o*-4-xyleneol (liquid).
9. 2-Hydroxydiphenyl (solid).
10. 4-Hydroxydiphenyl (solid).

group by the neighbouring groups decreases the strength of the hydrogen bridges which may be formed. With diphenylcarbinol and triphenylcarbinol (Fig. 4, Nos. 7, 8) this steric influence is well marked. In these connexions *o*-hydroxydiphenyl appears to be an exception, and will be discussed below.

When there are two hydroxyl groups in the molecule (Fig. 3, Nos. 6—10; Fig. 4, Nos. 6, 9—16) the dilute solutions again show the "normal" hydroxyl band at about 3615 cm^{-1} , but in the solid state a given compound may simultaneously show several "association" bands. When there are two neighbouring hydroxyl groups (Fig. 4, Nos. 9—16) the dilute solutions

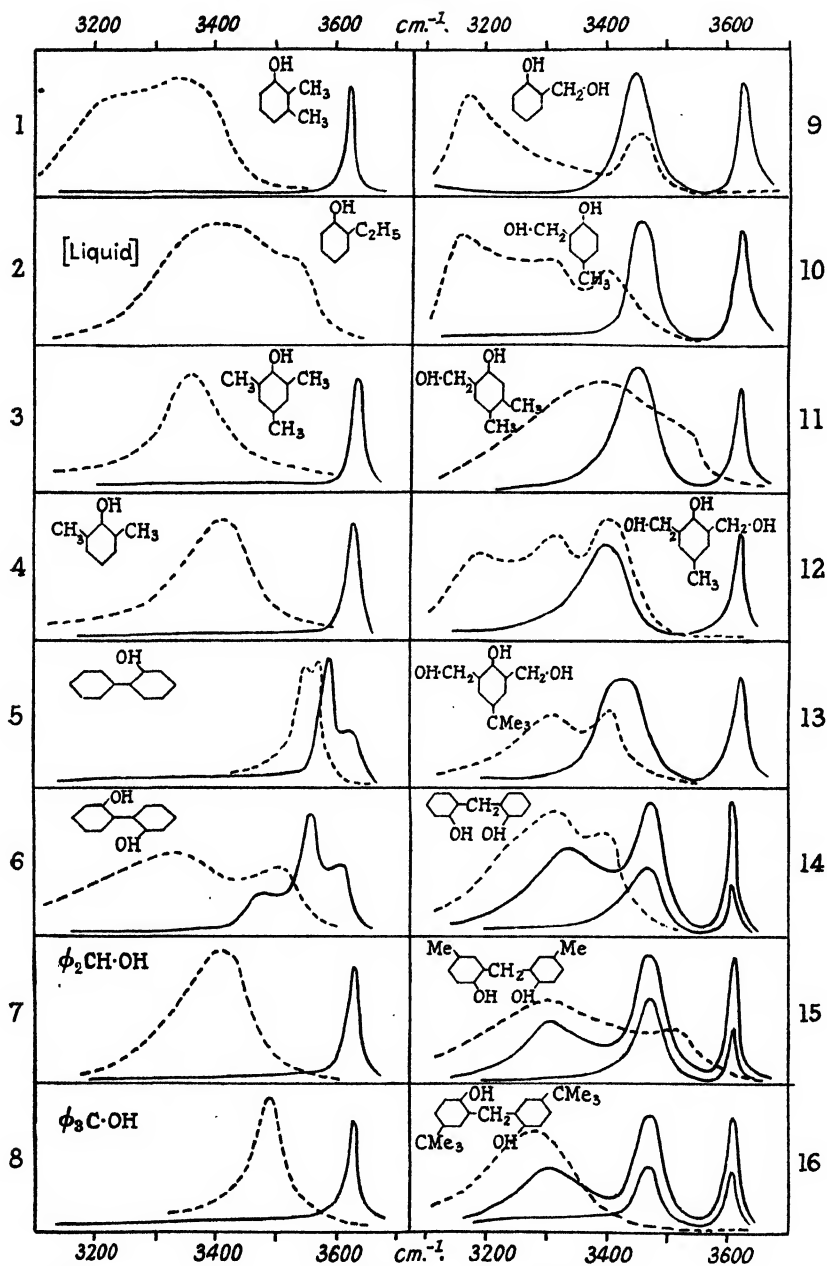
FIG. 3.



show, in addition to the normal hydroxyl band, another fairly sharp band at about 3450 cm^{-1} , which generally persists in the solid state. This band is sharper than the customary "association" bands, but behaves as if it were due to internal hydrogen bonding not markedly affected by dilution. Just as with *o*-hydroxydiphenyl already mentioned, so, too, 2,2'-dihydroxydiphenyl appears to be anomalous.

In the case of *o*-hydroxydiphenyl, a dilute solution shows the main hydroxyl band at 3590 cm^{-1} , although there is a weak shoulder in the usual position at about 3610 cm^{-1} . In the solid a close doublet appears at 3560 cm^{-1} . Reference to a scale model of the molecule suggests that the size of the OH group is such that the planes of the two aromatic rings may be slightly oblique to each other. In any case, however, the distance between the oxygen atom and the 2'-carbon atom is within the value which would allow of a hydrogen bond being formed of the

FIG. 4.

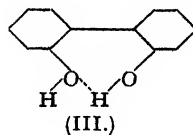
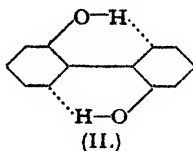
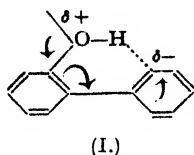


1. *o*-3-Xylenol.
2. *o*-Ethylphenol.
3. *Mesitol*.
4. *m*-2-Xylenol.
5. 2-Hydroxydiphenyl.
6. 2:2'-Dihydroxydiphenyl.
7. Benzhydrol.
8. Triphenylcarbinol.

9. *o*-Hydroxybenzyl alcohol.
10. 3-Hydroxymethyl-*p*-cresol.
11. 5-Hydroxymethyl-*o*-4-xylenol.
12. 3:5-Bishydroxymethyl-*p*-cresol.
13. 2:6-Bishydroxymethyl-*p*-tert.-butylphenol.
14. 2:2'-Dihydroxydiphenylmethane.
15. 2:2'-Dihydroxy-5:5'-dimethyldiphenylmethane.
16. 2:2'-Dihydroxy-5:5'-di-tert.-butyldiphenylmethane.

----- solid.
 ——— solution in CCl_4 .

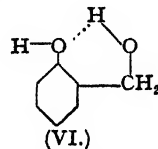
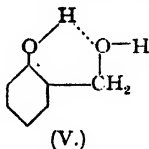
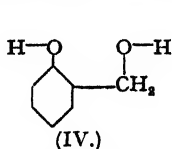
type $\text{O-H} \cdots \text{C}$. In this particular case the formation of such a bond might be assisted by the fractional charge which the 2'-carbon atoms may acquire owing to electronic displacements depicted in (I). The formation of $\text{C-H} \cdots \text{O}$ bridges has been established by infra-red and



other methods (e.g., Gordy, *J. Chem. Physics*, 1940, 8, 170; 1941, 9, 204, 215; *J. Amer. Chem. Soc.*, 1938, 60, 605; 1941, 63, 1094; Buswell, Rodebush and Roy, *ibid.*, 1938, 60, 252), and it is not unreasonable to expect $\text{O-H} \cdots \text{C}$ bonds in favourable circumstances. If there is internal bonding of this kind, it is not surprising to find only a small shift of the absorption band on passing from the solution to the solid. In this connexion, too, it is worth noting that *o*-hydroxydiphenyl melts at a much lower temperature than its *p*-isomer.

2:2'-Dihydroxydiphenyl in dilute solutions shows some similarities to *o*-hydroxydiphenyl. It may be noted that the strong band at 3560 cm^{-1} is due to internal bonding of the type $\text{O-H} \cdots \text{C}$, as in (II), the broad band at 3610 cm^{-1} to some unassociated hydroxyl groups, and the weak band at 3470 cm^{-1} to bonded hydroxyl group of the type shown in (III).

With dilute solutions of compounds containing two close hydroxyl groups, two sharp bands were found at about 3610 and 3450 cm^{-1} . The former must be due to free hydroxyl groups as in (IV). Internal bonding as in (V) or (VI) may give rise to the sharp band at 3450 cm^{-1} which is sometimes hardly affected, or only slightly displaced, on passing to the solid. In the solid state there is indication of intermolecular bonding giving broader bands at lower frequencies ($3200\text{--}3350 \text{ cm}^{-1}$), as well as the intra-molecular bonding.



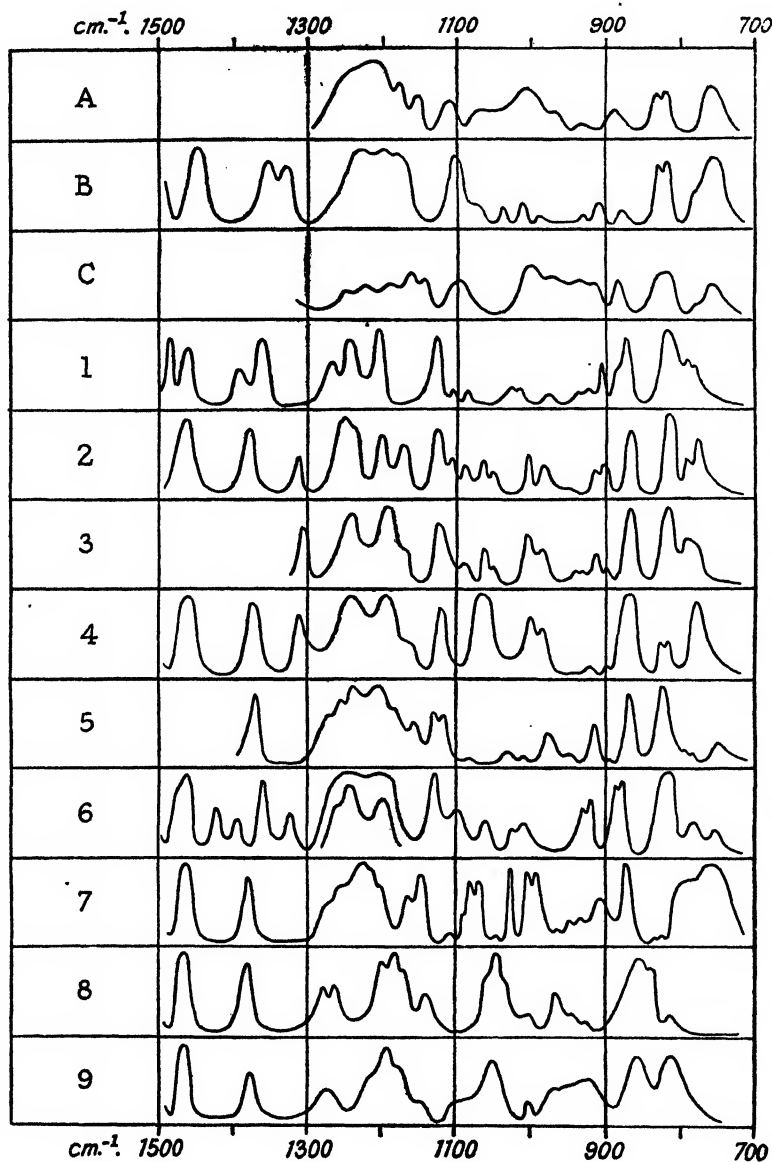
Some exploratory attempts have been made to measure the relative intensities of the bands due to the free and the bonded hydroxyl groups at different temperatures, since this should lead to a quantitative estimate of the strengths of the hydrogen bonds. The low boiling point of carbon tetrachloride makes it an unsuitable solvent, but carbon tetrabromide has been used in thickness up to 5 cm . at 3μ . The spectra of *o*-hydroxybenzyl alcohol in carbon tetrachloride at 20° , and in carbon tetrabromide at 100° , show a profound change in the relative intensities of the free and the bonded hydroxyl group bands. It is hoped shortly to extend these measurements by an improved method.

Fig. 5 shows the spectra between 700 and 1500 cm^{-1} of some resins formed by the condensation of phenols with formaldehyde or acetaldehyde at various stages of the condensation, and there are examples of pairs of resins made from the same starting materials but having different physical properties, e.g. (2) and (3) from *p*-tert.-amylphenol and formaldehyde. The samples were measured either as solid films made by melting and allowing to solidify between rock salt plates, or by grinding to a paste with "Nujol." Undoubtedly a little free phenol must have been present in some of the starting materials, and there are signs that small amounts were present in the final resins. This must be taken into account in drawing conclusions from the measurements.

Clear differences exist between the spectra of the phenol-formaldehyde resins at different stages of condensation. In particular, the two-stage fusible resin differs from the one-stage resin in having a stronger band at about 1105 cm^{-1} , and weaker absorption between 950 and 1050 cm^{-1} . The two-stage infusible resin shows the band at 880 cm^{-1} relatively more strongly, and has intense absorption between 900 and 1000 cm^{-1} . All the other resins show significant differences in the region $900\text{--}1500 \text{ cm}^{-1}$. For example, (2) and (3), novolacs of different melting point made from *p*-tert.-amylphenol and formaldehyde, differ in the region $1100\text{--}1300 \text{ cm}^{-1}$, and the resol (4) has a strong band near 1070 cm^{-1} which is probably connected with the CH_2OH group. The differences between the spectra of (8) and (9) reflect the different nature of the xylenols used in their preparation.

The spectral differences in the range 700—900 cm^{-1} are especially important, since as already explained the intense bands in this region may be associated with C-H deformations of different kinds of substituted benzene nucleus. In the one-stage phenol-formaldehyde resin the band

FIG. 5.

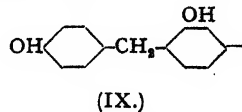
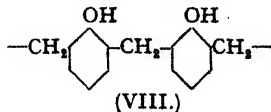
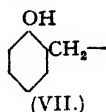


- A. Phenol-formaldehyde resin, one-stage.
 B. Phenol-formaldehyde resin, two-stage, fusible.
 C. Phenol-formaldehyde resin, two-stage, infusible.
 1. p-tert.-Butylphenol-formaldehyde, novolac.
 2. p-tert.-Amylphenol-formaldehyde, novolac.
 3. p-tert.-Amylphenol-formaldehyde, high m.p. novolac.

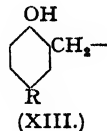
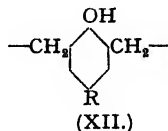
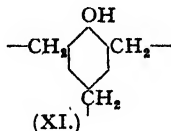
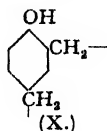
4. p-tert.-Amylphenol-formaldehyde, resol.
 5. p-tert.-Octylphenol-formaldehyde, novolac.
 6. p-tert.-Butylphenol-acetaldehyde, novolac.
 7. p- α -Phenylethylphenol-formaldehyde, novolac.
 8. Xylenol-formaldehyde, high m.p. novolac.
 9. Xylenol-formaldehyde, novolac.

at 750—760 cm^{-1} will be due to *o*-substituted nuclei, and to any residual free phenol. Such *o*-substituted groups will presumably be as in (VII), the end groups of a chain, and the intensity of the band suggests that such groups are relatively so numerous that the chain length must be

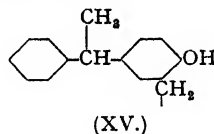
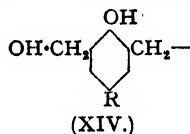
fairly short, say 4—8 aromatic nuclei. The weaker band at about 780 cm^{-1} in the two-stage resins is probably due to 1 : 2 : 3-substituted rings of the type (VIII). The bands at 815—



830 cm^{-1} probably arise from *p*-substituted rings such as (IX), or 1 : 2 : 4-substituted rings such as (X). The band at about 880 cm^{-1} may be due to tetra-substituted rings such as (XI), and it may be noted that in the two-stage infusible resin this band is strengthened, as would arise from further cross linking.



Resins (1), (2), (3), (5), and (6) all show strong bands at about 820 and 870 cm^{-1} . The latter can be correlated with tetra-substituted nuclei as in (XII), and the former with 1 : 2 : 4-substituted nuclei such as (XIII). With the resol from *p*-*tert*-amyphenol (4), the weak band at 820 cm^{-1} may arise because the end groups are of the type (XIV), rather than (XIII). The



resol from *p*- α -phenylethylphenol is peculiar in having no appreciable band near 820 cm^{-1} , and has intense absorption near 750 cm^{-1} and 790 cm^{-1} . The latter can be interpreted as arising from the monosubstituted phenyl group in (XV), and the strong shoulder at about 790 cm^{-1} from the 1 : 2 : 4-substituted rings. The xylenol resins also differ from the others in this region, as might be expected since the nuclei must in this case be either tetra- or penta-substituted.

These examples serve to illustrate how useful structural correlations can be made, but it would be premature to discuss them in greater detail until resins can be examined which have been made from purer starting materials and by controlled methods of condensation.

The resins differ, however, in one other important feature, namely, the position of the band near 3μ due to the stretching vibration of the hydroxyl group. All the solid resins show a more or less broad band due to the hydrogen-bonded hydroxyl group, but its exact position varies in the different resins between 3200 and 3550 cm^{-1} . Dilute solutions in carbon tetrachloride show a weak sharp band at about 3615 cm^{-1} due to unassociated hydroxyl groups, together with the association band found with the solids and lying in about the same position as in the latter case. The results are shown in Fig. 6. It is noteworthy that (10) and (11), both novolac resins made from *p*-*tert*-octylphenol and formaldehyde, have their bonded hydroxyl group bands at noticeably different frequencies.

The results show that in the resins there are hydrogen bridges of varying strengths. In some cases, more than one association band appears [*e.g.*, Fig. 6, Nos. (7), (1), and (2)]. This might arise from impurities in the starting materials, but is more probably due to different types of hydrogen bond within the same resin. With the exception of the weak band at 3615 cm^{-1} in dilute solutions there is a close similarity between the spectra of a solid resin and of its solution. This suggests that the majority of the hydrogen bonds may be intramolecular, which would agree with the comparatively low melting points of these particular resins, and also with the inactivity of their hydroxyl groups towards diazomethane. If this is so, one factor in the "curing" of the resins might be a change from intra- to inter-molecular association. In the final heating intramolecular bonds may be opened, and larger complexes formed by inter-molecular association. Whilst such changes may only be one factor in the "curing" process, it might cause a considerable rise of melting point and hardness quite apart from that caused by further chemical condensations. The differences in the strengths of the hydrogen bonds in the solid novolacs are to some extent paralleled by differences in their physical properties.

This was well marked in the resins (10) and (11) shown in Fig. 6. A more exhaustive and controlled survey of this question is desirable.

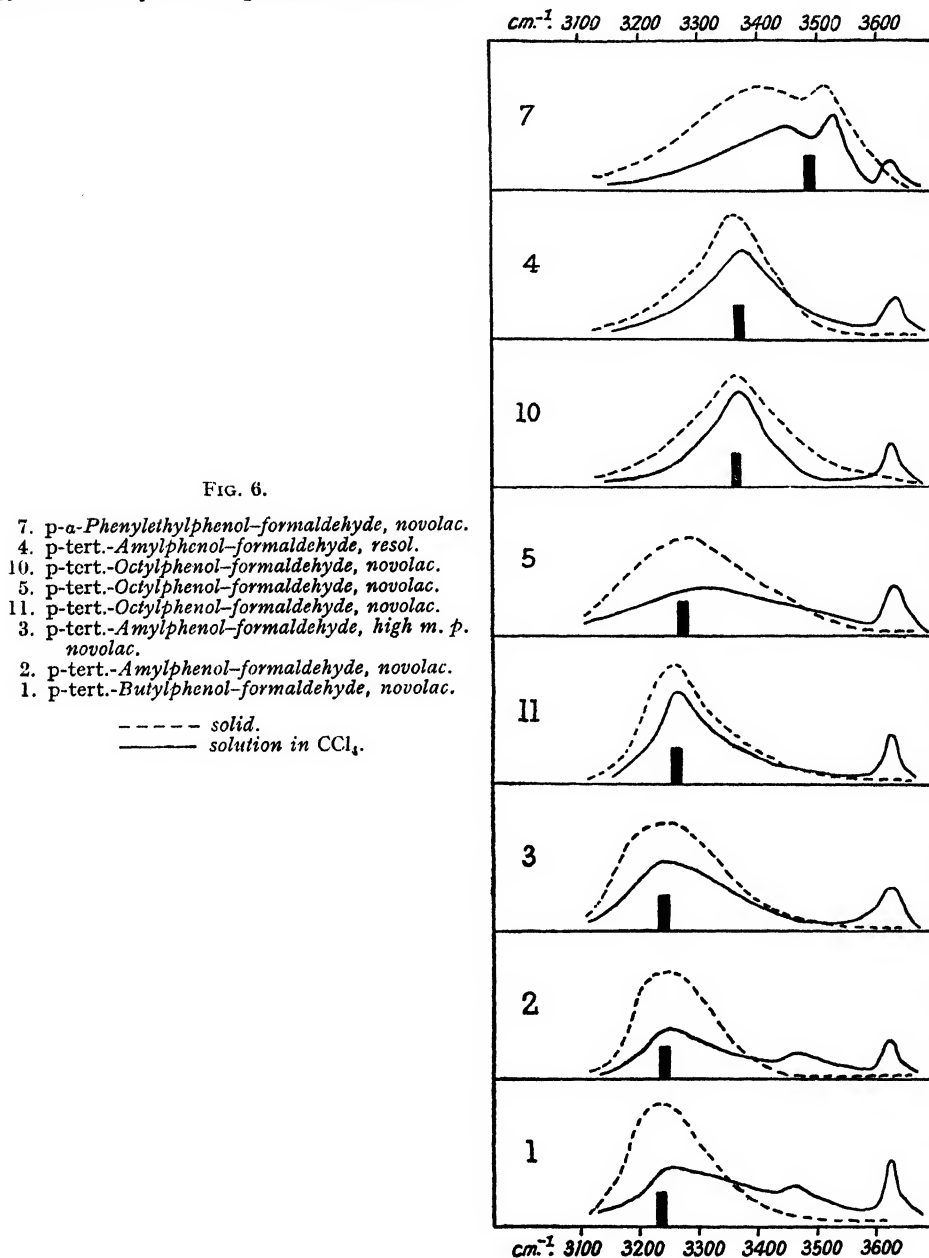


FIG. 6.

7. p-*a*-Phenylethylphenol-formaldehyde, novolac.
4. p-*tert*.-Amylphenol-formaldehyde, resol.
10. p-*tert*.-Octylphenol-formaldehyde, novolac.
5. p-*tert*.-Octylphenol-formaldehyde, novolac.
11. p-*tert*.-Octylphenol-formaldehyde, novolac.
3. p-*tert*.-Amylphenol-formaldehyde, high m. p. novolac.
2. p-*tert*.-Amylphenol-formaldehyde, novolac.
1. p-*tert*.-Butylphenol-formaldehyde, novolac.

We are grateful to the Government Grant Committee of the Royal Society for a grant in aid of equipment, and to the Department of Scientific and Industrial Research for a Maintenance Grant.

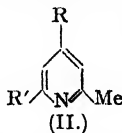
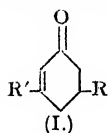
THE PHYSICAL CHEMISTRY LABORATORY,
OXFORD.

[Received, November 6th, 1946.]

NOTE.

2-cycloHexenones from 2-Methylpyridines. By ARTHUR J. BIRCH.

DERIVATIVES of several methyl-2-cyclohexenones were required for comparison with those obtained from the reduction products of methylanisoles and methyldimethylanilines (J., 1944, 430; 1946, 593). Ketones of type (I; R' = alkyl) have been obtained by the cyclisation of 1:5-diketones, but for the formation of type (I, R' = H) the more difficultly accessible 1:5-keto-aldehydes are necessary (cf. Koetz and Steinhorst, *Annalen*, 1911, 379, 20). Derivatives of both kinds of dicarbonyl compound have been obtained from 1:4-dihydropyridines (Shaw, J., 1937, 300), and it has now been found that reduction



of 2-methylpyridines with sodium and alcohol in liquid ammonia followed by refluxing with acid leads to hydrolysis of the dihydropyridine and cyclisation with direct formation of the cyclohexenone.

The 2-methylpyridine (10 g.) was reduced with sodium (5 g.) and alcohol (20 c.c.) in ammonia (150 c.c.) (see Birch, J., 1946, 595), water (150 c.c.) added, the product isolated by ether extraction, and refluxed for 6 hours with sulphuric acid (*d* 1.84, 15 c.c.) and water (50 c.c.), and the solution saturated with ammonium sulphate and extracted with ether. The ether solution was dried (K₂CO₃) and the product distilled.

Pyridine.	cycloHexenone.	Derivatives.
2-Methyl- (II; R = R' = H).	2- (I; R = R' = H), b. p. 164—168°, 12%.	2: 4-Dinitrophenylhydrazone, m. p. 164—165°.
2: 4-Dimethyl- (II; R = Me, R' = H).	5-Methyl-2- (II; R = Me, R' = H), ¹ b. p. 179—183°, 15%.	2: 4-Dinitrophenylhydrazone, ² m. p. 145—146°; semicarbazone, ³ m. p. 175—176°.
2: 6-Dimethyl- (II; R = H, R' = Me).	3-Methyl-2- (I; R = H, R' = Me), ⁴ b. p. 194—197°, 17%.	2: 4-Dinitrophenylhydrazone, m. p. 174°; semicarbazone, m. p. 200—202°.
2: 4: 6-Trimethyl- (II; R = R' = Me).	3: 5-Dimethyl-2- (I; R = R' = Me), ⁵ b. p. 205—210°, 30%.	2: 4-Dinitrophenylhydrazone, m. p. 163—164°; semicarbazone, m. p. 176—177°.

¹ Found: C, 76.4; H, 9.3. Calc. for C₇H₁₀O: C, 76.4; H, 9.1%.

² Found: C, 53.7; H, 4.8. C₁₃H₁₄O₄N₄ requires C, 53.7; H, 4.8%.

³ Found: C, 57.5; H, 7.7. Calc. for C₉H₁₂ON₃: C, 57.5; H, 7.8%.

⁴ Found: C, 76.1; H, 9.1. Calc. for C₇H₁₀O: C, 76.4; H, 9.1%.

⁵ Found: C, 77.8; H, 9.5. Calc. for C₈H₁₂O: C, 77.5; H, 9.7%.

The yields of cyclohexenones are poor, and the method has no advantage over the standard ones for their preparation in quantity, except where the alkylpyridine is readily available and other methods are difficult, *e.g.*, 5-methyl-2-cyclohexenone from 2: 4-dimethylpyridine (cf. Koetz and Steinhorst, *loc. cit.*). For the preparation of small amounts of derivatives the method is rapid and convenient.

This work was carried out during the tenure of an I.C.I. Research Fellowship.—THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [Received, November 19th, 1946.]

*Address on the Occasion of the Centenary Celebration of the
Chemical Society.*

By THE PRESIDENT, PROFESSOR C. N. HINSHELWOOD, M.A., Sc.D., D.Sc., F.R.S.

THE observance of anniversaries and centenaries is dictated by a deep-seated instinct. How far this in its turn is inspired by a feeling for the magic of numbers and awe at the vast cyclical processes of Nature, I do not know, but, however that may be, these recurrent occasions for retrospect and prospect are assuredly felt to be significant and moving.

The character of the thoughts and emotions which they arouse will in some measure depend upon the attitude towards history adopted by the participants. To some, history is as a play that is ended: to others, as a chart on which they hope to read the future from the past. But to everyone, I suppose, the centenary of a scientific society must bring a message of some kind.

There are few dramas as enthralling as the struggle for the secrets of reluctant Nature, and few fields in which the future beckons so insistently as in that of scientific thought.

We are celebrating the centenary, not of a discovery, not of a person, but of a Society, and this circumstance reminds us that thoughts and inventions are in a considerable measure the products of particular historical settings. For our purpose, therefore, we cannot reflect upon the history of chemistry in the past century in England, or speculate upon its probable future, except in relation to the people who made it and are making it, and to the general conditions of their lives.

Not only does the pious memory of our Founders, benefactors, and predecessors (both the recognised and the unrecognised great men) bid us consider the human as well as the purely intellectual story, but it is doubtful whether any other approach would be more than an abstraction with the limited validity which abstractions have.

You see what deep philosophical questions are raised by the major theme: the relation of the scientific and the humane; the nature of history and the possibility of extrapolation and prediction; piety towards the past, expectations from and duties toward the future. I feel called upon to remind you of these themes, even though I cannot possibly do justice to them.

The Chemical Society was founded in the year 1841. The England in which it came into being stood on the threshold of one of its greatest eras of expansion, but no one at the time could know of this, and to many the prospect must have appeared sombre and even fuller of uncertainties than that which confronts us today. The dislocations caused by the Industrial Revolution were all too obvious, but the fruits of progress were still to be gathered. The lot of the impoverished manual workers was wretched in the extreme, the scandals of child labour in coal mines, potteries, and other industries were coming to light, but the Factory Acts were not yet passed, the agitation and distress connected with the Corn Laws coloured the political scene, and the demand of workers for a better mode of life expressed itself in the Chartist movement and broke forth into riots which to many people suggested that society was on the verge of revolution and disruption.

Queen Victoria was on the throne, but the splendours of her era were yet to be, and the great movements of her time would only have been discernible to those of unusual penetration. The worst social conditions depicted in the writings of Dickens still prevailed.

There was nothing in the obvious character of the time to announce a period of intellectual flowering, and yet it was just then that many learned societies, including our own, came into being. Scientific studies in England were hardly in any clear way the product of their age, and sprang more from the learned curiosity of amateurs than from the conscious needs of society. There were practically no laboratories for chemical research, and little or no University instruction in chemistry.

The chemical stage was set as follows. In 1841, the time which had elapsed since the "chemical revolution" of Lavoisier was almost exactly equal to that from the discovery of radioactivity to the present day. Chemistry as a science was then as old as is now the new nuclear alchemy upon which we believe the future so largely to depend. It is difficult today for a scientifically educated person to realise how profound was the change of thought which followed the publication of the Lavoisier treatise. It represented a complete philosophical re-orientation of ideas on the nature of substance. Two Englishmen in very different ways had played parts of the first magnitude. Priestley, whose house was wrecked by a mob, had made the discovery which opened the way for Lavoisier, and Dalton, living in an obscurity which astonished his foreign visitors, had formulated the theory upon which all future development was to depend.

Between the time of Dalton and the foundation of the Chemical Society the great forward sweep of organic chemistry had begun, but in this the English school had played little part, as was explicable in a country which tended to produce a few of the finest flowers of science, art, and literature without any very vigorous general growth of leaf and root. At the moment of our foundation Dalton was still alive, but Liebig, who visited England at about this time, found little in the world of chemistry to inspire him. Yet Faraday was at the height of his powers and his great work on the laws of electrolytic action was already accomplished. Its full implications were far from obvious to his contemporaries, and indeed the confusions which Avogadro's paper of 1811 might have cleared away still clouded chemistry. On the Continent the great battle between the rival interpretations of the structure of organic compounds was at its height.

At about this time much was being done in England to lay the foundations of physical chemistry, not only by Faraday with his work on the liquefaction of gases and on electro-chemistry, but also by the original and versatile Thomas Graham, first President of the Chemical Society.

Such was the chemical scene at the time of our foundation.

Let us now, after the manner of the dramatist, raise the curtain at successive intervals of a generation and see what transformations have been brought about.

1861, twenty years after the foundation, was, as it happens, the year of Prince Albert's death and of the outbreak of the American Civil War. The early dislocations caused by the Industrial Revolution were now largely righted, the conditions of labour had improved, steamships and railways were in rapid development, the era of prosperity symbolised by the Great Exhibition of 1851 was well launched, and the great intellectual movements of the Victorian age were under way. Herbert Spencer's advocacy of scientific education sought to justify in theory what the foundation of the College of Chemistry in 1847, Owens College, Manchester, in 1851, and the Oxford laboratories in 1861 were gradually implementing in practice. "The Origin of Species" had appeared in 1859, and the materialist trend of thought was evident. Chemistry had seen two decades of steady progress but had been on the whole unshaken by revolutionary changes. Cannizzaro's paper of 1858 had removed one of the major obscurities, and Frankland and Kekulé had placed structural chemistry on a firm foundation. In this country Hofmann, Mansfield, Williamson, and Frankland are seen among the outstanding figures of the period. Chemistry in England was still mainly the affair of the amateur. Indeed, in 1867 the only technical education in Leeds with its quarter of a million inhabitants was provided by one teacher who worked in a cellar and held a class in chemistry, receiving a grant of £11 a year for the purpose. Nevertheless the *Journal of the Chemical Society* from its early years had attracted contributions from the eminent chemists of the Continent, and the names of Liebig and Bunsen are in evidence.

Another twenty years pass and many momentous changes have occurred. The historical background shows political democracy in England in full stride with widened franchise and a sweeping increase in general literacy: it shows the decline of agriculture in its most disastrous phase, and the British primacy in the manufacturing export trade just about to decline from its height. The early signs of major world troubles are already discernible: the rank weeds of bureaucracy are breaking through the soil, and since 1870 the world has learnt from Prussia that war on the national scale has possibilities hitherto unexploited. The curse of conscription already lies on Europe. Disraeli has died, and Karl Marx lives in London. In some respects the Victorian age has passed its zenith, and some of the brightest stars have set: Dickens, Mill, and Clark Maxwell are gone, and Darwin's work is over. Although there have been important events such as the founding of the Cavendish laboratory in 1871, the position of scientific studies in the Universities is still feeble, and even now the great discoveries and inventions continue to come from men who are self-taught and have received little formal training.

Some of the great trends of chemistry are reflected in our *Journal*. One of the most splendid phenomena had been the flowering of the great tree of organic chemistry. To this science the contribution of England was honourable but limited. At the time in question the great name of Perkin appears currently, first the father, then the son. The science of physical chemistry is well launched, and perhaps the papers of Harcourt and Esson on the "Course of Chemical Change" are among the most characteristic of the contributions from this country. We must note the immense clarification which chemistry had by now received from the Periodic Law, observing with satisfaction that Newlands had done so much to initiate this by a paper read to the Chemical Society in 1866, but with regret that this paper was never published.

The *Journal* of the year 1881 is interesting. Boron hydride is described, while experiments on the synthesis of ammonia and discussions of absorption spectra show the approach of modern

times. But one publication above all shines like a beacon. This is the great Faraday lecture of Helmholtz, where for the first time the full implications of Faraday's laws are revealed and the way is opened for the whole modern electronic theory.

As an example of the delay which may attend the exploitation of valuable discoveries a passage in the Presidential Address of Roscoe in this year speaks for itself. "The researches of Captain Abney have been continued with conspicuous success, and have given birth to a discovery of the highest interest and of the greatest possible promise. This is no less than a distinct physical test of the existence in organic compounds of the organic radicals, and a means of recognising the chemical structure of an organic compound by means of the spectroscope. This result, which naturally opens out an entirely new field for investigation, and effects for the organic metals that which ordinary high temperature spectrum analysis does for the inorganic metals, is accomplished by photographing the absorption spectra of organic compounds in the infra-red part of the spectrum. In these invisible portions, characteristic and distinct absorption lines and bands occur for each organic radical. . . . This investigation is still in its infancy, but one of greater importance to chemists has seldom, if ever, been communicated to the Society."

The next scene presents a mottled picture of sun and shade. In 1901 the death of Queen Victoria symbolised the end of an epoch. It was a time of intellectual and social unrest and uncertainty: agriculture had collapsed, industrial struggles had acquired a new bitterness, the tide of the new popular journalism was rising in a strong flood, and the administrative machinery of the country was elaborated beyond what had ever been known. Some trade prosperity and the residues of a romantic imperialism imparted their diverse glammers, and a brilliant Court was about to lend an appearance of solidity to an age which the first German War was destined to bring to a catastrophic end.

By this time the health of chemistry in Britain was much more robust, and schools of research were gradually coming into being in many of the Universities. Tilden in 1904 told the Chemical Society that he considered the science to be flourishing. A glance at the *Journal* of 1901 certainly shows a great variety of activities, which range over investigations on alkaloids, bacterial actions, optically active nitrogen compounds, absorption spectra, and the synthesis of methane. A paper by Lapworth marks the beginning of that detailed interpretation of the inner mechanism of reactions which has been one of the great British contributions to organic chemistry in the present century. It is indeed appropriate that the Faraday lecture to be given during the present celebrations is devoted to the exposition of this powerful theme.

Radioactivity had been discovered in 1896 by Becquerel, and in 1902 the first of Rutherford's great contributions makes its appearance in the *Journal*. A measure of the excitement of the times is conveyed by the words at the end of the second contribution of Rutherford and Soddy:

"Nothing can yet be stated of the mechanism of the changes involved, but whatever view is ultimately adopted it seems not unreasonable to hope that radioactivity affords the means of obtaining information of processes occurring within the chemical atom."

The transformation by 1921 was colossal indeed in every aspect of life: profound political changes, an unprecedented degree of mechanism, and all the febrile aftermath of what then counted as the greatest war in history. People were more conscious than ever before of international and economic problems. The scene shifts from a national stage to a world stage.

The war of 1914—1918 had brought profound changes to British chemistry. It has often been called the chemist's war. Unprecedented needs of explosives, chemical warfare agents, and other products of industry had forced an improvised expansion, which, by a fortunate dispensation of providence, gradually merged into an orderly and continued evolution. In the following decade there is a history, which may be followed with a degree of sober satisfaction, of the creation of a new chemical industry, of the expansion of University research, of the founding of research institutes, and, not least, of the establishment of the most excellent relations between industrial and academic chemistry. These are one of the happiest auguries for our uncertain future.

Taking a glance at some of the subjects represented in the *Journal* of 1921, we find, in the first place, papers belonging to the aftermath of the chemist's war: on explosives and mustard gas, and on the sorption of gases: we are reminded of a major revolution in science by Aston's lecture on mass spectra. On the physical side, colloidal electrolytes, heterogeneous catalysis, and photochemistry are coming into prominence, and Brönsted's paper on salt effects typifies not only the transition from the older to the newer theories of solution, but also the abiding international character of our chemical literature. On the organic side, Perkin's papers on the

alkaloids, harmine and harmaline, belong to the culmination of one great tradition in organic chemistry, while a newer tradition, that of studying function as well as structure and of bringing physical ideas into intimate relation with the study of organic substances, is illustrated by papers on the influence of substituents on the character of benzene compounds and by a series of Ingold's early papers on questions of reactivity. Vernon's work on tellurium derivatives reminds us of the contributions which this country has made to stereochemical problems, especially through the researches of Mills, past President of the Chemical Society.

If we pursue our theatrical fancy to the end and raise the curtain for a last time on the actual centenary date of 1941, it discloses a scene of chaos and destruction. Two decades of fruitful progress seem to have been brought to a tragic end. In some ways the two decades had been among the most productive that chemistry had known. The constitution of natural products had been brilliantly revealed, and in this connexion the names of two Presidents of the Society—Haworth and Robinson—are outstanding. Modern theories of valency had brought an immense clarification into the whole system of inorganic chemistry: the subtleties of organic behaviour had been penetrated, and the intimate mechanism of chemical changes in general stood largely revealed. There had been a powerful cross-fertilisation of chemistry with physics and mathematics. And on the human side the developments were no less vigorous: vastly increased support of research in the Universities, a flood tide of advance in the chemical industry, and, not least, the growth of co-operation between the centres of pure science on the one hand and the great industries on the other, which was of incalculable significance.

As I have remarked, the way in which all this is assessed depends upon a philosophical attitude. One view of history sees the course of human affairs as a chaotic sequence of accidents, the results of unpredictable and indeed often unknowable contingencies: the other sees an orderly and inevitable flow of events in well-marked channels. In that great work "War and Peace" Tolstoy defends and illustrates the second thesis, discounting the influence of great men, and maintaining passionately that the fate of nations evolves naturally out of their essential nature.

All men of science are familiar with those controversies in which the arguments on both sides seem unanswerable: and they know that in the end the contending parties are realised to have seen not truth and falsehood but two aspects of a larger whole. A scientific analogy helps to resolve the conflict about the nature of history.

The evolution of material systems is governed both by those thermodynamic factors which determine equilibria and define the extent and direction of possible changes, and, differently but equally powerfully, by the kinetic factors which determine when and where the changes are initiated and with what speed they progress. The former depend upon average conditions such as temperature and pressure, the latter upon chance fluctuations of energy, highly localised and intense departures from the average. Without these exceptional events the system remains inert. But on the other hand, no fluctuation, however violent, causes its evolution in a direction different from that required by the thermodynamic state. So it may well be in affairs: the exceptional event, the rise of the great man of thought or action, determines time and location, but, for the exceptional to take effect, the average must be in a condition to respond.

In the survey of the century, therefore, one may try to discern the essential trends, to which great events and personalities are related more as occasions than as causes.

As far as chemistry is concerned the history of at any rate the first half of the century has been very much the affair of the individual. The great names—Davy, Faraday, Dalton, Graham, Newlands, Frankland, Perkin—do not seem to bear any special relation to their environment, and might seem to support the purely sporadic view of history. And yet certain general currents are discernible in the contribution from this country. Perhaps one of the deepest and strongest has been the evolution based upon an intuitive sense of the electrical nature of matter. By much more than a play of fancy a genealogy can be traced, through Davy who found the key to the phenomena of polar combination, Faraday, Crookes whose instinct guided him to the study of "radiant matter", Townsend and J. J. Thomson who infuse new blood from physics, to the modern schools of Lapworth, Robinson, and Ingold, who have carried the electrical conception into the subtlest regions of organic chemistry. Nor should I omit in this connexion to mention the scholarly studies of Sidgwick, another past President of the Society, which have done so much to clarify the vast field of inorganic chemistry. This line will almost certainly continue, but how, or where, is as indeterminate as the position of a single electron in an atom.

A collateral line is formed by those who, speculating on the nature of matter, were vouchsafed a glimpse of a promised land into which they did not enter fully—Prout, Newlands, Crookes.

The final conquest of that land came only when the armies of physics and of chemistry joined forces in the victorious advance of Rutherford and Soddy, Rayleigh and Ramsay, J. J. Thomson, Aston and Moseley.

In contrast with the imaginative quality of these men, another of our strongest traditions has been that of empirical observation, unguided by much in the way of theory. This has expressed and illustrated both a national strength and a national weakness. From the days of Priestley onwards, it has led to factual discoveries of the first importance, and produced experimenters second to none in such men as Dewar, Dixon, and Bone, but it has not created schools, and its positive achievements have occasionally been lessened by a mistrust of theory so healthy as almost to discourage understanding. But the impact of the two opposing schools has been unquestionably fruitful, and has sometimes added to the gaiety of nations.

Other recurrent themes can be traced throughout the century: on the one hand a sense of the mystery and wonder of chemical change, and on the other a joy in precise measurement for its own sake—two contrasted but equally important motives in the development of physical chemistry, which reflect the blend of the romantic and the practical in the make-up of so many Englishmen. Affinities could be traced throughout the period, as between the work of Graham and that of Berkeley and Hartley, or between the spirit of Harcourt and Esson and that of various modern schools. And yet, the purely personal character of much of the great work could equally well be illustrated by innumerable examples, such as Perkin's famous discovery of mauve, Dewar's observations on specific heats at low temperatures, or Crookes's studies of the rare earths.

The truth is, I think, that the more easily distinguishable threads have been woven more by what is common in the intellectual make-up of the people, than by a direct and conscious tradition. There are men who, placed in almost any circumstances, will mould them to something great, and it is such men predominantly whom we have to commemorate, at any rate in all but the last two decades of the century. The breeding of such men is not likely to change in any rapid way, but the nature of the society into which they are born is changing before our eyes.

One of the unmistakable trends of the past century has been the successive decline of different aspects of individualism: the independent craftsman, the aristocratic politician, the empire-building explorer all departed from the scene. In science a similar trend has been visible though at a lag of several decades. At the time of our foundation the stage is dominated by the amateur, whether a Cavendish or a Faraday: later the individual is more and more frequently dependent upon the University or technical college, small and independent but none the less a community. Then the great research associations appear and the State subsidy becomes indispensable. Two great wars intensified and accelerated the collective process in the world of science until today we are faced with the problems presented by vast industrial research laboratories and by state enterprises undertaking work which is inconceivable without the co-ordinated efforts of hundreds of men of science. The great question is: what is to be the fate of the individual in the world which has emerged?

In this matter something of an ideological battle has been engaged, and since the question is one of moment for the future of an independent scientific society, I propose to say a little about it, in as objective a manner as possible.

May I, for this purpose, introduce an analogy between human affairs and certain scientific laws? The particles composing matter are endowed with individual motions which would lead to complete chaos but for attractive forces constraining them at times into orderly configurations. The two conflicting tendencies are, of course, what men of science know as the entropy factor and the energy factor. It is the balance between the two which governs all the rich complexity of chemistry and physics, and determines that measure of effective action called free energy. Were there maximum entropy and complete chaos the world of phenomena would be much the poorer, but were there the rigid constraint which the energy factor alone would impose things would be as bad or worse. Nobody who has thought about science can fail to admire the art with which Nature interweaves her two great themes. When molecular chaos is set in order it is only at a price, but price and value are astutely bargained. So it must be in human affairs.

Complete individualism means chaos, which is only given form by something analogous to an energy factor—by State compulsion, or by powerful emotional forces. If any of these controls are applied too vigorously the result is order indeed but the order of utter stagnation. Just as Nature strikes her subtle balance, so it must be here. Nothing is less fruitful than doctrinaire argument about freedom and planning. The vast achievements of military regimentation in

wartime have been cited as examples for peace, but in this it is forgotten that results in limited spheres have had to be bought with an utter disregard of cost, whether of money, happiness, or life.

The problem is not to propound facile doctrines, but by hard and detailed thinking in every possible sphere to find those mechanisms and those techniques which in combination lead to the greatest measure of effective action.

A hundred years ago we saw an individualist society faced with the task of controlling the industrial revolution: at the beginning of a new century we face a task which seems even greater, that of preventing an organised society from turning individuals into slaves. The problem involves the relation of the State to science, of the industries to the Universities, the organisation of research laboratories, and indeed the relation of every man of science to the laboratory in which he works and to the science as a whole.

Those who call themselves planners are often, I think, not conscious enough of the art and effort involved in large-scale action. Even with the most admirable motives and goals, operative complexity often brings frustration. There is need for a complete new science, a kind of biological and psychological statistical mechanics to clarify these matters. The beginnings of it exist. Indeed we have seen one gigantic manifestation of directed human activity in the evil arts of the late rulers of Germany, whose ingenious mechanisms were applied in opposition to truth and justice but might have been used to better ends.

This thesis will be accepted readily enough by the exponents of what are now called social studies, but we may be told that the organisation of affairs must be placed in the hands of specially trained humanists, and that the scientific man should be confined to the rôle of an advisory expert. Such a tradition has of course tended to grow up in some of the public services. But one can say with conviction that its persistence will be unfortunate and its extension disastrous. It is like a separation of the heart from the brain and of the mind from the body. The man of science must himself handle the human problems, and, in scientific affairs, nobody but the man of science can do it. On the whole the Universities and the great chemical industries are aware of this, and the excellent relations which have been growing up between them will exert a powerful influence for good, and are of happy augury. But eternal vigilance is the price of these things. At every level in every organisation where men are engaged in scientific pursuits those in charge must continue to wrestle with the problems of combining liberty with order to the end of finding that course which is humanly as well as technically the most effective.

One very welcome sign of the past few years has been the increasing number of scientific papers published from the chemical industry. These are clear and welcome evidence that the leaders of that industry are showing understanding of the intellectual needs of the men who serve it. One can only hope that the whips of commercial secrecy will not be succeeded by the scorpions of military security.

Looking to the future of chemical research, one can confidently foresee an era of great technical progress. The powerful organisations which will ensure this are already in operation. The relevant problems of pure science will also be explored on a scale which has hitherto been undreamt of. Such matters as thermodynamic and kinetic studies on polymers, biological studies on chemotherapeutic agents, and scores of others could be cited to show how the approach is changing from the sporadic and the amateur to the thorough and the professional. All this leads to new knowledge of inestimable value, and in this field also progress seems assured.

But of that most important kind of new knowledge, that which does not seem to relate to any existing field, it is harder to speak on the basis of anything but faith. And yet in this knowledge lies the true seed of the future. It will come only from the least conforming of minds, and the discoveries of the greatest ultimate moment are the least likely to have been favoured by official encouragement or support. They must be like the flowers of the poet

"daffodils,
That come before the swallow dares, and take
The winds of March with beauty."

We may well ask whether the winds of future Marches may not be more intolerant than those of the past.

There is no royal road to be followed into the future. In the scientific and social history of the past century the picture has been one of light and shade, ebb and flow, and enormous uncertainties crowned by miraculous progress. On this scene men of all kinds have laboured for the science of chemistry. Today we honour them. There is no reason to suppose that

their qualities have not been inherited. The stage is changed and the parts are different, but the actors are very much the same.

It is still the individual who really counts, but his problems are different. Faraday's genius overcame lack of education and lack of facilities. These are handicaps from which he would be very unlikely to suffer today. The Faraday of tomorrow will have by his own methods to break through the trammels of an over-organised society : and for this it may well be that he will need something more of the quality of a Nelson.

Nothing has ever yet contained the great river of knowledge. Though Archimedes was slain, Galileo persecuted, and Lavoisier condemned, it has flowed over or around every obstacle which stupidity, indifference, or malevolence have created.

In the old eastern story a debate arises as to what is the strongest thing in the world, and in the end this is recognised to be the truth. "As for the truth it endureth and is always strong : it liveth and conquereth for evermore. . . . Great is truth and mighty above all things." Whatever clouds may seem to lower over the new century, this is the great light which shines on it.

But this faith does not obviate the necessity for continuous detailed effort. If it is based upon an extrapolation from the past, that past is one in which people were ready to struggle and endure. It is incumbent on us to consider what stands before our Society and what policies that Society should pursue.

There is one which stands in the centre of and indeed includes all other policies, and that is to maintain the prestige of chemistry as a pure science. It is right that the Chemical Society should occupy a central position in the world of chemistry. I have referred to the increasing complexity of this world, with its multiplicity of organisations. But by common consent new knowledge is the life blood of it all, and the heart should be the Chemical Society itself. Of the relations between the great chemical industry and the Universities I have already spoken, and gratitude must be expressed for the humane policy of so many leaders of that industry. But it remains for the younger chemists in it to take an ever more active part in the publication and discussion of new knowledge. Provision for this is one of those problems where the scientific and the humane are inseparable.

Relations between chemistry and its neighbour sciences—physics, mathematics, and biology—are now so close that the frontiers are practically abolished and the joint discussion of common problems will be of increasing importance.

All this raises a practical question of the first magnitude, that of adequate facilities for meeting. I feel a little ashamed that on this great occasion we should receive our guests in alien halls, however hospitable they may be. I should like to hope that before long a statesmanlike solution to this problem will have been found.

Important as buildings may be, our publications are still more so, and in the eyes of posterity the Society of today will be judged more by the quality of the work which it publishes than by any other criterion. As Shakespeare tells us, the immortality conferred by black ink is greater than that of gates of steel or rocks impregnable. It has been a sad economy which has lavished money upon so many objects while neglecting the means of scientific publication. We must continue to struggle against this unhappy policy and hope that it will pass, never to return.

Among the traditions upon which we look back with pride is that of the international character of the Society. I am happy to say that as the result of a special Centenary Appeal for the purpose this valuable element in our activity will be strengthened, and that we now have the means of bringing foreign men of science to take part more often and more fully in our doings. There can be no question of the great benefit which chemists in this country will derive from the arrangement.

And now to the conclusion of the whole matter. What the Society is and must continue above all else to be is a fellowship of those who share the love of chemistry, that most splendid child of intellect and art. Chemistry provides not only a mental discipline, but an adventure and an æsthetic experience. Its followers seek to know the hidden causes which underlie the transformations of our changing world, to learn the essence of the rose's colour, the lilac's fragrance, and the oak's tenacity, and to understand the secret paths by which the sunlight and the air create these wonders.

And to this knowledge they attach an absolute value, that of truth and beauty. The vision of Nature yields the secret of power and wealth, and for this it may be sought by many. But it is revealed only to those who seek it for itself. Its pursuit has united the predecessors whom we commemorate : it will unite our successors for as long as the spirit of man endures.

*A Century of Chemistry.**

A LECTURE DELIVERED ON FEBRUARY 19TH, 1947, AT A JOINT MEETING OF THE ROYAL SOCIETY OF ARTS AND THE CHEMICAL SOCIETY TO COMMEMORATE THE CENTENARY OF THE FOUNDATION OF THE CHEMICAL SOCIETY.

By Sir HAROLD HARTLEY, K.C.V.O., M.C., F.R.S.

THIS evening Fellows of the Chemical Society have made a pilgrimage, not, it is true, a very long or hazardous one, although in this year of grace 1947 we shall return by torchlight, to John Street, Adelphi, to the Royal Society of Arts, the birthplace of our Society. We have come like the pilgrims of old, who made much longer journeys, in a spirit of piety to the place that holds such a high place in our memories, to pay our homage to the Society that gave us hospitality for our first meetings. It was on February 23rd, 1841, thanks to the initiative of Robert Warington and the kindness of his friend Arthur Aikin, formerly the Secretary of the Society of Arts, that twenty-five chemists, including Aikin, met in this building to consider founding a Chemical Society, and here its first regular meeting took place on March 30th, 1841.

The Society of Arts had been established for nearly a century, and its Secretary Aikin was a very remarkable man. He had been one of the founders of the Geological Society, but his abiding enthusiasm was for chemistry, thanks to his early friendship with Priestley, and he became the first Treasurer of the Chemical Society and its second President. So we started life with a close personal link between us.

However, the fledgling Society soon wanted to try its wings, and in six months it left the nest to go to the Westminster Literary and Scientific Institution in Leicester Square. There was some fear too that chemical experiments might not be welcomed in these august precincts. But migration was found to have its drawbacks; oddly enough there were difficulties about heating; they missed this warm nest, and in 1842 the Society was back in John Street, where it enjoyed the hospitality of the Society of Arts at the modest rent of £25 a year until 1849. The Annual Reports reveal the general satisfaction of the members with this arrangement, and indeed in 1844 the Council reported "that the arrangement . . . continues to be satisfactory to both parties, and especially to ourselves, as we have not only acquired a convenient habitation, but have avoided the expenses included in the word establishment so often ruinous to young Societies". Happy indeed is the institution that has no overheads!

But by 1849, when the Society got its Charter, it had outgrown the limits of your kind hospitality, and needed rooms for its library and collections, which it found in the Strand. And so ended this happy connection between us, for which the Chemical Society will always be most grateful.

This year in July the Chemical Society is celebrating, somewhat belatedly, its centenary, and tonight we come here to commemorate its first meeting in the building where it took place. It is my privilege, in this joint meeting, to try and sketch the achievements not of the Chemical Society, for that is the task of the President, but the achievements of our science since 1841—what it has done, with the help of its sister sciences, to give man control over the materials on which his well-being depends, and to throw light on the complexities of living matter.

Chemistry in 1790—1840.

1841—just over half a century since Lavoisier had given chemistry its modern form in his great Treatise of 1789, his autobiography of one of the simplest and most decisive revolutions science has known. Lavoisier applied to chemistry not only the balance but, being skilled in affairs, the method of the balance sheet. The idea of the chemical equation dominated his mind, and his first chemical equation dealt, as the Bible tells us, with one of the earliest and one of the most significant chemical reactions known to man. It runs:

Le moût de raisin = acide carbonique + alkool.

We owe to Lavoisier the first clear distinction between physical and chemical change. With Laplace he laid the foundations of thermochemistry. We owe to him the idea of organic combustions by which he was the first to determine the quantitative composition of the products of living processes. When he was guillotined in 1794 he was setting his course towards the Atlantis of biochemistry.

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After Lavoisier in 1808 came Dalton with his Atomic Theory. It was one of those flashes of genius that crystallises an idea that had been floating in men's minds for centuries, and gives it the simple concrete form that makes it a powerful instrument in the hands of mankind. Lavoisier's analyses and his nomenclature could then be translated into atomic formulæ, the chemist's shorthand.

The next landmark was Davy's verification of Lavoisier's prediction of the existence of the alkali metals; their isolation by electrolysis laid the foundation of electrochemistry and of the association of chemical affinity with electrical charges. Davy also redressed the balance of Lavoisier's over-estimate of the central position of oxygen by showing that the essential element in an acid is hydrogen and not oxygen.

And then, just as chemistry was attracting more and more attention and new chemical facts were being discovered so rapidly, came the Swede, Berzelius—the most massive figure in the whole of its history. In a few years he determined single-handed with amazing skill and sagacity the atomic weight of every known element and the composition of many compounds, thus giving added reality to Dalton's theory. He too substituted for Dalton's geometrical symbols the initial letters of the names of the elements, which we use to-day. Berzelius had an encyclopædic mind, and he embodied in ten volumes the whole compass of chemical knowledge enriched by many of his own discoveries. Conservative as to the ideas which had served him well, he had the intuition to see where there was a common pattern in diverse chemical phenomena, and we owe to him the generalisations of isomerism and catalysis and their names.

For twenty years Berzelius was the accepted authority and the influence he exerted through his Annual Reports on current literature and through his friendships with the younger generation of chemists was immense. Meanwhile the younger men like Liebig, Wöhler, and Dumas were laying the foundations of organic chemistry by making series of derivatives from natural products with inorganic reagents. The new facts they discovered were difficult to reconcile both with the dualism and the theory of radicals which Berzelius had inherited from Lavoisier, and with his own view of the dependence of chemical affinity on electrically charged atoms. By 1841 his authority was seriously challenged. His formulæ were discredited, even his atomic weights were largely replaced by equivalents, and there was a drift from theory towards empiricism.

Founding of the Chemical Society.

So the Chemical Society was founded at a most opportune moment, when the number of young men doing research was rapidly increasing and the opportunity for discussion and publishing their results was badly needed. For the next twenty years chemistry was to be in a state of flux, without any generally accepted theory. It was a time of bitter controversy, when the older chemists resented criticism and the younger men like Gerhardt and Laurent suffered persecution for their views. In their heroic battle against authority, which they ultimately won, Pope's lines, often spoken in jest of our profession, came literally true :

" The starving chemist in his golden views
Supremely blest, the poet in his Muse ".

Laurent died as a result of privation.

From 1840 to 1860 the work of most outstanding chemists lay in organic chemistry. It was a period of rapid growth, when experiments were almost bound to lead to discoveries. Each chemist had his own theory of which he was tenacious, as it meant much to him; it was in a sense the scaffolding which enabled him to make his own contribution to the structure of chemistry. And so it is not surprising that by 1859 a whole page of Kekulé's text book was filled by the different formulæ proposed for such a simple substance as acetic acid.

As the technique of organic reactions was gradually developed, each year brought an increasing harvest of new compounds and there was a growing need for some new system of classification to include them all. Laurent and Gerhardt, with their logical French minds, had each been seeking a new basis of classification along rather different lines, and their partnership led eventually to Gerhardt's type theory in which all organic compounds were derived by substitution from four simple inorganic substances, hydrogen, water, hydrochloric acid, and ammonia. Gerhardt's theory was an unconscious recognition of the different combining powers of the atoms and groups, and led inevitably to Kekulé's theory of atom linkage. It had been a long struggle, and Laurent died in 1853, but Gerhardt lived until 1856 to taste success and see his views adopted by the younger chemists.

The early meetings of the Chemical Society during that stormy period must have been lively and stimulating, with men like Lyon Playfair, Graham, Brodie, William Odling

(Gerhardt's *l'ami Odling*), and Williamson, to whose classic paper on ether and alcohol Gerhardt owed so much. And there were in London during those years young German chemists of great ability—Kolbe came in 1845, to infect the young Frankland with his interest in the synthesis of organic compounds from simple molecules. Hofmann came in the same year to teach at the new College of Chemistry in Oxford Street, and Kekulé in 1853 as assistant to Stenhouse, the Chemist to the Mint. Kekulé often said that his theory of the structure of organic compounds started in his dream about atoms on the top of an omnibus one night between Islington and Clapham Road where he lodged. So in those days London and the meetings of the Chemical Society which took place in this building from 1841 to 1849 were a focus of chemical thought.

Cannizzaro and Kekulé.

These two decades of uncertainty and divided opinion ended almost abruptly after 1860, thanks to the constructive thinking of two men. In 1860 the first international conference of chemists was held at Karlsruhe at Kekulé's suggestion, with the object of arriving at some agreement about atomic weights and molecular formulae. Nearly all the active workers in each country were present, but as at other international meetings progress was slow. Committees were appointed which grew larger and larger, there was jockeying for position and eventually the Congress broke up in a chilly mood, having accomplished practically nothing. But copies of a thin paper-covered pamphlet on atomic and molecular weights by Cannizzaro, the Professor of Chemistry at Palermo, were given to some of the delegates. His exposition of the existing difficulties and their solution by the consistent use of the laws of Avogadro and Dulong and Petit was so clear and convincing that as Lothar Meyer said when he read it "the scales fell from my eyes, doubts disappeared and were replaced by a feeling of certainty". It was not long before there was a general agreement among chemists about the weights of the atoms and the number of atoms in a molecule, which, as Kekulé had foreseen, was a necessary preliminary to a general theory of the constitution of molecules.

The other decisive factor was Kekulé's theory of atomic linkages, each atom having a definite combining power—hydrogen one, oxygen two, nitrogen three, and carbon four. On this basis, recognising that atoms of carbon, unlike other elements, could unite to form stable chains, or rings like the six-membered benzene molecule, Kekulé was able to assign definite structures to organic compounds, and this gave an immense impulse to the advance of organic chemistry.

When these major controversies were over, chemistry advanced rapidly on a wide front in the years from 1860 to 1900 which form the next epoch.

Organic Chemistry, 1860—1900.

Kekulé's theory of atomic linkage had presented chemists with an almost unlimited number of possible arrangements of carbon atoms in straight or branched chains, or in rings with intermediate links of other atoms which could also form part of closed-ring structures. These possibilities chemists were quick to explore, both by building up new molecules by synthesis in the laboratory, and by trying first to ascertain the molecular structure of natural products and then to synthesise them in the laboratory. Outstanding examples of this were the syntheses of alizarin in 1869 and of indigo in 1880. In this way many new compounds were made and described, and the technique of organic reactions was continuously extended. Between 1856 and 1910 the number of known organic compounds increased from 3,000 to 200,000.

In this period of rapid development there was one episode of outstanding importance, the simultaneous recognition by van't Hoff and Le Bel of the need to take into account the arrangement of the atoms in three dimensions. Kekulé had realised this, but he was sceptical about the power of chemistry to reveal the actual structure of the molecule, although he thought physics might do so. Pasteur in 1845 had already proved from the rotation of light passing through them that in certain cases the same atoms could form either a right- or a left-handed molecule. Van't Hoff and Le Bel showed that this was due to the presence of one or more carbon atoms combined with four different groups which could be arranged spatially in right- and left-handed forms. In addition, the arrangement of the atoms in space could account for a number of other unexplained phenomena. All their predictions were quickly verified, and since 1874 stereochemistry, the arrangement of the atoms in space, has been a potent factor in the progress of organic chemistry.

During these years it was in Baeyer's laboratory that most of the foremost organic chemists served their apprenticeship. It was there that Emil Fischer, the younger Perkin, Willstätter, and many others learnt the simple technique of the test tube and glass rod with which so many

discoveries were made before the elaborate technique of modern organic chemistry became necessary. The sugars, the terpenes, and the alkaloids yielded the secrets of their structures. Some of the many new compounds that were synthesised were only of scientific interest, while others yielded new dyes or new perfumes or new drugs like eucaine and veronal, so called because Emil Fischer happened to wake up and look out of his carriage window at Verona after a visit to Baeyer to discuss its properties.

Inorganic Chemistry, 1860—1900.

The advance of inorganic chemistry naturally took a different course. In 1860 sixty-four elements were known and many attempts had been made to classify them in families with very limited success. When agreement had been reached as to the relative weight of the atoms a new line of attack was opened, and in 1864 both Newlands and Lothar Meyer pointed out that if the elements are arranged in the order of their atomic weights, elements recur at regular intervals with similar properties, apparently belonging to the same family. Four years later Mendeléeff, using more accurate atomic weights, developed the Periodic System in much greater detail and predicted by means of it the properties of three undiscovered elements which were missing from the system. The accuracy of his predictions was shown by the discovery of gallium in 1875, scandium in 1879, and germanium in 1886. The invention of the spectroscope by Bunsen and Kirchhoff in 1859 had given chemists a powerful new instrument, and the discovery of further new elements, rubidium, caesium, and thallium, soon followed with its aid, to fill other gaps in the Periodic Table of the elements. But even though it provided a basis for the classification of the elements in families, many puzzling problems in the Table remained unsolved.

Physical Chemistry, 1860—1900.

Meanwhile the influence of physics on chemistry was being felt more and more, both in the use of new techniques like the spectroscope and in various applications of physical theory. Here again van't Hoff was the pioneer in a dual attack by applying both molecular theory and the laws of energy to the analysis of chemical phenomena. The laws of energy or thermodynamics are laws of experience like Newton's law of motion, independent of any hypotheses as to the nature of matter, and affording therefore a useful test of the truth of such hypotheses and of classifying and forecasting certain chemical phenomena. Willard Gibbs had been the forerunner in this field in 1876—1878, but van't Hoff was the first to show the wide applications of thermodynamics to chemistry. At the same time he was analysing the kinetics of chemical reactions and the nature of chemical equilibrium in the light of molecular theory, and showed their dependence on the behaviour and properties of the individual molecule. Thus in the 'eighties a new subject, Physical Chemistry, was taking shape, especially in the field of solutions, where Arrhenius gave it a fresh impulse with his theory of electrolytic dissociation which related the electrical conductivity of solutions to the dissociation of molecules into electrically charged ions. That again had applications in many fields, and with the help of Ostwald and Nernst physical chemistry quickly became a powerful new instrument.

And so in the 'nineties, when I and my contemporaries were learning chemistry, organic chemistry gave us a tidy logical picture in which the agreement between properties and structure showed clearly that the model represented a close approximation to the truth. In physical chemistry we got a picture of the dependence of chemical reactions and equilibria on the kinetics of the individual molecule or ion, and of the value of thermodynamics in giving generalised laws independent of any theory. Inorganic chemistry was more difficult; by then there were so many isolated facts to be remembered, and while the Periodic Table was a great help, there were many anomalies still to be explained.

Nineteenth-century chemistry had been based on the Newtonian atoms, those small, hard, indivisible, elementary particles of which all matter was thought to be composed, and its development was mainly that of an experimental science. The whole picture of molecular constitution had been built up by inference from macroscopic experiments, and there were no means of investigating the fine structure of matter to give some clue as to the nature of the atoms, of their chemical affinity that caused their reactions, or of their valency that determined their combining powers. The evidence of their spectra certainly suggested that their structures were far from simple.

Then suddenly there came a rapid succession of discoveries that threw an entirely fresh light on the whole subject and by 1914 had given chemists a new conception of the unity and sub-mechanics of their science.

The Period of Great Discoveries, 1895—1913.

In 1897 J. J. Thomson discovered the negative electron, showing that electricity is atomic and that the electron is common to all atoms. Becquerel had already discovered radioactivity in 1896, and Madame Curie isolated radium in 1898. These discoveries, together with Rutherford and Soddy's systematic investigation of radioactive charges, gave the first clue to the nature of the atom.

Roentgen's discovery of X-rays in 1895, with wave-lengths approximating to atomic dimensions, in the hands of von Laue and the Braggs proved a most powerful means of investigating the arrangement of atoms and ions in crystals and later the arrangement of the atoms in the molecule.

In 1911 Rutherford's discovery of the dimensions and nature of the nucleus led to his theory of the nuclear atom consisting of a small central positively charged nucleus with electrons rotating in orbits around it. Moseley in 1913, by examining the frequencies of the X-rays emitted by different atoms, proved that there are ninety-two elements with ordinal numbers corresponding to the number of charges on the nucleus, thus throwing an entirely new light on the Periodic Table. As a proof of the thorough way in which nineteenth century chemists had done their work, it is worth noting that of that complex and hitherto mysterious group of elements, the rare earths, fourteen had been separated and recognised as elements before Moseley's law was known, leaving only one of extreme rarity to be found.

The full significance of Rayleigh and Ramsay's discovery in 1895 of argon, the first of the rare gases, followed by Ramsay's discovery of the rest of the family, was now apparent. The arrangement of the electrons in their atoms was so stable that they showed no tendency to combination, and this was the basis of G. N. Lewis's and Kossel's theories of valency as dependent on the stability of an octet of electrons in the outer shell of the atom.

In 1901 Planck had shown that radiant energy had a certain atomic character, as it could only be emitted and absorbed in discrete quanta, the size of which was proportional to the frequency of the vibrations. The fundamental significance of this discovery to chemistry was not at first obvious, until Bohr in 1912 showed that the application of the quantum theory to the electron orbits in Rutherford's atoms could explain the structure of their spectra, the actual wave-lengths of which could be calculated in simple cases.

Then, just as all the tools for future development were in the chemist's hands, came the war of 1914, the first chemists' war, in which chemistry played a vital part in making explosives, in making synthetic products to counter the effects of a blockade and in the military use of gas and smoke. The effect of this was to intensify the effort directed to chemical research after 1918.

Chemistry in the Inter-war Years.

Demobilised from their war activities, chemists returned to their laboratories with fresh zest to take up again the work that had held so many exciting prospects in 1914. I remember Rutherford saying to me in 1919: "What's the use of going back to chemistry when Bohr will soon be able to calculate anything you can find out?" But Rutherford was the last person to dissuade anyone from experimenting, and it was in his own laboratory that the science of nuclear physics was born.

During the inter-war years chemistry has progressed with amazing speed, and its influence has been felt increasingly in the sister sciences of physiology, botany, agriculture, and geology. The main factors in its progress have come from physics, both from new physical techniques and from new physical theories. Progress has been on such a wide front that it is impossible to summarise, but there seem to me four outstanding achievements in the fields of atomic and molecular structure, of nuclear physics and isotopes, of the kinetics of chemical action, and of the organic chemistry of living processes.

Atomic and Molecular Structure.

Chemistry owes to physics the detailed knowledge that we now possess of the structure of molecules, derived from measurements of their X-ray diffraction, electron diffraction, Raman spectra, dipole moments, and their spectra from the infra-red to the ultra-violet. There has been a continuous development both of the technique and of its application in each field since 1919. Thanks to this we now know the distances between the centres of the atoms in any linkage, the position of the atoms relative to one another, the nature of the linkage, the heat of formation of the linkage and its resistance to deformation.

Simultaneously with this advance on the experimental side there has been a remarkable

development on the theoretical side which has stimulated experiment and has explained the causes underlying the behaviour of the atoms and molecules.

Till 1925 the Bohr-Rutherford atom held the field, the positively charged nucleus with electrons rotating round it in various orbits. From the purely chemical side it gave a qualitative explanation of the valencies of the elements, it distinguished between electrovalent, covalent, and co-ordinate links, and it explained most of the regularities of the Periodic System. It gave a quantitative basis for calculating the spectra of atoms and simple molecules, and with the hypotheses of electron spin and molecular vibration it accounted for the fine structure of spectra and their behaviour in a magnetic field.

But difficulties arose with the model atom as the electron sometimes appeared to behave as a particle and at others as a wave motion, a dilemma that was the basis of Heisenberg's Uncertainty Principle. The difficulty was solved by the new calculus of quantum mechanics, in which the properties of the atom are described by equations which admit of no simple physical interpretation such as a model. The test of their validity is the wonderful accuracy with which they can predict the behaviour of single atoms. Unfortunately in more complex systems great mathematical difficulties are involved in a rigid solution, and various methods of approximation have to be adopted. However, in spite of this, quantum mechanics has provided a new stimulus and a new interpretation in many fields, particularly in regard to valency. It enables the direction of the valencies of any atom in space to be calculated, and provides a much more subtle differentiation of the various types of linkage. The periodicity of the properties of the elements with increasing atomic number can be shown to be a necessary consequence of the geometrical symmetry of the electron fields. It explains too the quantum restrictions as a necessary consequence of the wave characteristics of the electron.

Isotopes.

The nucleus itself is mainly the concern of pure physics, but there is one important exception, the existence of isotopes, atoms with the same atomic number but with nuclei of different mass. By means of his mass spectroscope Aston showed that the chemical elements are nearly all mixtures of isotopes, and by measuring the amount of each present and its atomic weight he explained why chemical atomic weights are so far removed from whole numbers. The actual separation of the isotopes with identical chemical properties by physical means was one of the most laborious experimental problems with which chemists have been faced.

But a new significance was given to isotopes when the physicists found it possible by bombarding atomic nuclei with various particles to transmute them and often to produce isotopes with radioactive properties differing from those of the parent atom. Quite apart from their therapeutic importance, such isotopes could be used as tracer elements in chemical reactions and in living processes to track down the course followed by the atom in question.

Physicists also discovered the particles of which the nucleus is composed, the positron, the positive equivalent of the electron, and the neutron, whose unique properties as a projectile in nuclear bombardments makes possible the utilisation of atomic energy.

The Kinetics of Chemical Change.

This brings me to the next main field of progress, the kinetics of chemical reactions. It is generally true to say that no phenomenon is as simple as it seemed to the original discoverer, and of nothing is this so true as of the equations used to represent chemical reactions. Only last year our President's Bakerian Lecture was devoted wholly to the complexities of that first schoolboy equation: $2\text{H}_2 + \text{O}_2 = 2\text{H}_2\text{O}$.

The investigation of reaction rates has given scope for much ingenious experimental and mathematical treatment. It has involved the study of the lives of the individual molecules, the circumstances under which they can acquire a critical amount of energy, the effect of radiation, the effect of catalysts, and the significance of chain reactions. Great progress has been made, which has given us a much more intimate picture of the actual mechanism by which chemical reactions take place. The results are of profound interest for both theory and practice, as so often it is the rate of change that determines what is possible.

Organic Chemistry.

And lastly there is organic chemistry, when we must go back to where we left it about 1900. Its outstanding achievement has been the light it has thrown on the great systems of the materials and processes of living organisms. Organic chemistry has thus returned to the task for which

it was originally equipped by Lavoisier and for which he meant to use it, the discovery of the chemical reactions of the living body. Its success has been to reveal their complexity. With the techniques that have been developed by organic chemists for over a century they can now break down or build up the most complex structure of carbon atoms and the groups attached to them with a certainty that leaves no doubt as to what that structure is.

Here again physical methods have played an important part. X-Ray analysis of crystalline or regularly orientated material has revealed the details of its atomic and molecular structure. Infra-red spectra have made possible the identification of minute quantities of material differing only in small details of their structure. The modern methods of chromatography, the selective adsorption of substances in various media, allow of the separation of the constituents of complex mixtures available only in small quantities which otherwise could not be resolved. The ultra-centrifuge too has helped in the separation of complex molecules and the determination of their molecular weights. The technique of microchemistry, the handling and analysis of small quantities of organic material, has made possible the investigation of substances available only in small quantities and quickened the pace at which investigations can proceed.

The problem for the chemist, in conjunction with the physicist and the biologist, is to unravel the processes by which Nature builds up the structure of living organisms, and provides the materials that discharge the functions of their various parts.

The plant is the first stage in Nature's economy, as plants alone can assimilate the carbon dioxide of the air and nitrogen from inorganic sources and synthesise from them the carbohydrates, fats, and proteins that form the food of other organisms. The first success of chemists in this field was the determination of the structures of the simple plant products, such as the sugars, vegetable oils and fats, essential oils like the terpenes, rubber, alkaloids, and various dyestuffs and colouring matters like the anthocyanins. Many of these were synthesised in the laboratory, and X-ray analysis has confirmed the correctness of the structures assigned to them on the ground of chemical behaviour. A comparison of these structures shows that Nature makes use of the economy of prefabricated construction, as many of them are built up by different arrangements of the same groups of carbon atoms. Thus the carbohydrates are all built up of chains of six carbon atoms, but C_3 may be an intermediate stage in this grouping, as the groups $C_6 - C_3$ and $C_6 - C_3 - C_6$ frequently occur in plant products. The vegetable fats and oils are mostly built up of C_6 units forming chains containing twelve, eighteen, or thirty atoms, joined together by the C_3 of glycerin. The structural units C_6 and C_3 recur again in a number of substances where the chain of six carbon atoms has been converted into a ring as in the oil of cloves and similar substances. Two $C_6 - C_3$ groups provide the skeleton of many others, and with the addition of C_6 the skeletons of the catechins and anthocyanins. The aromatic oils, resins and rubber have been formed by a different route; they are built up from a C_6 unit with a branched carbon chain which may either condense to rings like the terpenes or polymerise to a long chain as in rubber.

But in spite of these regularities we have little knowledge of the methods by which Nature marshals these units in the living cell. Her catalytic methods are so specific in their actions and work so cleanly compared with ours that she is able to marshal these structural units to form complex molecules under the influence of surface forces exerted as it were by a template of existing molecules. The ease and certainty of Nature's methods is so intriguing and tantalising to the chemist working in a non-living environment.

It was quickly realised that many of the main constituents of living organisms, the polysaccharides and the proteins, had vastly greater molecules than these simple plant products, and here again X-rays have rendered decisive help. Cellulose, for instance, was found to consist of hundreds or thousands of glucose residues united in a straight chain, and forming the chain bundles which are the predominant structural element of the plant kingdom. In rubber the long carbon chains are folded higgledy-piggledy around one another, straightening when the rubber is stretched and giving it its elasticity. The discovery of formaldehyde phenol plastics by Baekeland in 1909 soon resulted in the synthesis of similar giant molecules in the laboratory and the study of their behaviour. Carother's classical investigation of the linkages which would produce these giant molecules led directly to the discovery of nylon, a nitrogenous synthetic fibre that is competitive with Nature's products.

Of all these giant molecules the proteins, which in one form or another enter into almost every living process, are the most significant. Emil Fischer's pioneer investigations showed that they all consist of various amino-acids linked together to form long chains. X-Ray analysis revealed the regular order in which the amino-acids alternate in the chains of different proteins and the position in space of the side groups, the projections from the chains that determine so

largely the specific properties of each. The proteins are divided into two great families, the fibrous and the globular, those in which the chains are extended like fibroin, the spider's web, and those in which they are coiled in a regular manner like albumin and hæmoglobin. The former class has again two main families, the keratin-myosin-fibrinogen group, including wool, hair, skin, nails, whalebone, muscle tissues, and the coagulating constituent of blood, and the collagen group including tendons, connective tissue, and cartilage. The knowledge of their chemical structure reveals something of the principles of Nature's engineering, of the way in which she provides for the necessary mechanical properties of the parts of an organism. And further it is beginning to throw light on the processes of growth, the synthesis of giant molecules by contact catalysis in living matter.

Great advances have been made in our knowledge of enzymes, those complex colloidal catalysts formed by living cells which enable the chemical changes that accompany and condition living processes to take place rapidly at ordinary temperatures. The isolation of some of them like urease, trypsin, and pepsin in a crystalline form was a great achievement. Some have proved to be pure proteins, while others, such as those responsible for the oxidation of food in the body, are proteins associated with various complex groups which can act as oxygen acceptors.

Then there are substances such as the vitamins, hormones, and auxins, small quantities of which exert such an immense effect on living functions. Vitamins are essential to normal life and healthy growth, and are all derived from foodstuffs. Their identification has played an important part in the modern treatment of nutrition, and the constitution of most of them is now known. Hormones are the chemical messengers, produced in one part of the body and exerting a most potent influence on others. Some of them, such as the sterols, and the active principles of others, such as adrenalin and thyroxin, have been isolated; their structures have been determined, and some of them have been synthesised. The knowledge gained in this way has been of the greatest value in curative medicine.

Lastly, there are the viruses, those minute carriers of disease that have been so hard to track down and isolate. Some of them have now been obtained in a crystalline form and have been shown to be nucleoproteins.

In addition to throwing light, in these and many other ways, on the complex molecules and the complex secrets of the chemical reactions on which the existence of life is dependent, chemists have synthesised many new substances which have important biological applications. Ehrlich's discovery of salvarsan in 1910 was an outstanding triumph. Its name "606" emphasises the number of attempts before a molecule was found that would destroy the spirochæte of syphilis without killing the patient. Later came the sulphonamides with their specific reactions against certain types of bacteria. Their power of stopping growth suggests that they are absorbed on the catalytic surfaces in place of some of Nature's prefabricated units of similar shape, and thus prevent the completion of the pattern and the formation of a new molecule. Their action has been likened to the jamming of a lock by a key that does not quite fit.

D.D.T. and gammexane come in another category. They are synthetic products of outstanding effectiveness in killing insect pests without hurting men or animals. Similarly a range of substances has been found which will kill weeds (dicotyledons) without damaging the growing crops which are monocotyledons.

One of the greatest triumphs of chemistry in the chemotherapeutic field has been the isolation of penicillin, and the elucidation of its structure, the last details of which were revealed by X-ray analysis, and finally its synthesis.

All these examples, and they are but a few of many, go to show what an effective instrument chemistry has become, working with her sister sciences in revealing both the possible combinations and permutations of the elements of which the world is made, and the nature of the processes associated with living organisms. But in addition, chemists have a great record of achievement in the application of all this accumulated knowledge to the service of mankind. And this brings me to the progress of chemical industry during the last hundred years.

Chemical Industry.

Our industry is, I know, of special interest to the Royal Society of Arts with its wonderful record of almost 200 years of activity devoted to the encouragement of the practical applications of scientific discovery. The progressive stages of civilisation have in fact been largely conditioned by the materials available to mankind. From the Bronze Age to the present age of

light alloys and plastics there has been a steady advance in the exploitation of natural materials to serve the needs of man, and in this the chemist has played the decisive rôle.

Chemical industry in 1841 was still in an embryo stage; it had not yet felt the effects of the great industrial expansion of the nineteenth century, or of the impact of science on industry. It was mainly concerned with the manufacture of acids, alkalis, and mineral salts, with the extraction of natural products like sugar and dyestuffs, and with various fermentation processes.

The first major development came from the progress of organic chemistry. Perkin's discovery in 1856 of mauve, the first synthetic dyestuff, started a new industry. One result was the first displacement of a natural product, when alizarin was synthesised in 1868, and the synthetic material quickly supplanted the cultivation of madder. Baeyer's synthesis of indigo in 1880 again led to the gradual displacement of the indigo crop.

With the rapid advance in the discovery of improved and faster colouring matters and the discovery of synthetic drugs like phenacetin and sulphonal, the organic industry grew rapidly. Although it had started in this country with Perkin, and Germans like Caro and Otto Witt came here to serve their apprenticeship, it was not long before Germany had secured the lead, mainly owing to her lavish investment in research. The scientific basis on which the organic industry had developed undoubtedly had a considerable influence on the development of the chemical industry as a whole.

In the heavy chemical industry the decisive episode in this country was I think the courageous and far-sighted decision of Ludwig Mond and John Brunner in 1872 to use the Solvay process for making soda. Their means were slender and several firms had already had to abandon the process. But Mond saw its possibilities, and for the first two years at Winnington he watched the process by day and night. The scientific control of the plant by which he achieved success and his skill in plant design marked the birth of chemical engineering in this country.

Other major factors were now at work to expand the scope of the industry. First came the demand for artificial fertilisers to meet the food demands of the rapidly growing industrial population. Then the availability of electrical energy from the dynamo gave a new impetus to the use of electrolytic methods to produce metals like aluminium, magnesium, and sodium, and alkali and chlorine, and of the electric furnace to make calcium carbide and other products.

The demand for explosives and the invention of gun cotton, dynamite, and high explosives built up another section of the industry. The peaceful uses of cellulose products—nitrocellulose, cellulose acetate, and viscose—provided another field of development, and in each new field the links between science and industry were drawn closer.

The successes of chemical engineering were achieved by plant design and process control. The design of plant was based on accurate quantitative knowledge of the reactions concerned, on securing maximum heat economy, on the use of an ever-increasing range of anti-corrosive materials, and on the use of the most efficient catalysts. Continuous control of processes was obtained by recording instruments at each stage and by analysis. The study of catalysis led to revolutionary changes first in the manufacture of sulphuric and nitric acids and ammonia and later in the whole range of the industry. The catalytic hydrogenation of vegetable oils was an outstanding contribution towards the supply of the world's demand for fats.

Then came the war of 1914, in which the chemical industry became almost a decisive factor by the production of explosives and fertilisers. In fact, without the Haber process for making ammonia, the blockade would quickly have compelled Germany's surrender. The war thus demonstrated the strategic importance of the chemical industry. To quote a sentence from the report of the Mission which I had the privilege of leading in 1919 to investigate the war uses of the German chemical factories: "In the future it is clear that every chemical factory must be regarded as a potential arsenal, and other nations cannot, therefore, submit to the domination of certain sections of chemical industry which Germany exercised before the war. For military security it is essential that each country should have its chemical industry firmly established". The lesson we learnt then was not forgotten.

As in pure chemistry, the inter-war period was a time of rapid development. The earlier development of synthetic chemistry had largely been in competition with Nature. Steinmetz, the genius of Schenectady, once said to the head of the I.G., "Bosch, I know you can make indigo cheaper than God, you may some day make rubber cheaper than God, but you will never make cellulose cheaper than God".

With the discovery of plastics and the vast possibilities of the synthesis of large molecules there has been some competition with natural products, such as nylon with silk, and synthetic rubber with the plantation product, but much progress has also been made in processing and

upgrading vegetable products, such as cellulose, starch, and vegetable oils, and in the use of farm by-products. The processing of foodstuffs, including crop drying, is another field in which chemical industry and agriculture are establishing a new community of interest. These developments are of great significance, as it means that industry is drawing increasingly on the revenue account instead of the capital account of the world's resources for its raw materials.

I must not omit, however, some reference to the remarkable technical progress of the petroleum industry in the inter-war years. The refining of crude oil was revolutionised by the use of catalysts, and most recently by the use of the so-called fluid catalyst, small particles suspended in a current of the reacting gases. In addition to making petrol of high octane value and other fuels, a new industry has been built up on the hydrocarbon gases from the cracking process and the natural gas from the oilfields. From them an immense variety of chemicals are now made, such as *isooctane*, synthetic rubber, and solvents of all kinds. Under the pressure of autarchy oil was made from coal, by hydrogenation and by the Fischer-Tropsch process, which is now expected to produce petrol and hydrocarbon gases at a price competitive with crude oil, starting from natural gas and using a fluid catalyst.

Once again we have seen how war has tested the resources of the chemical industry, when it proved its ability to produce, at a cost, whatever was needed from the available raw materials, whether it was aviation fuel, rocket fuel, synthetic rubber, or synthetic fibres. Chemical engineers too played a great part in the vast organisation, with all its attendant difficulties, necessary to separate the quantities of uranium 235 and plutonium in the state of purity needed for the atomic bomb. And their work opens up a vista of possibilities of the use of atomic energy for peaceful purposes.

Conclusion.

Thus in its industry, as in pure science, chemistry has a great record of achievement. Looking back at the state of knowledge when our Society was founded here in 1841, we see a wonderful century of progress. And in this the Fellows of the Society have always played a leading part. But it is well to remember that that swift advance has depended on the efforts of men in many countries working together with a common aim, with no tariffs or visas to hinder the flow of new ideas.

And I cannot help reflecting on the contrast between this record of achievement and the sorry state of the world to-day. Is it not paradoxical that with the understanding we have won of Nature's secrets, with our power to control nature in action, that the majority of mankind should still be suffering from malnutrition and many from endemic disease? This seems to me a challenge to science and not least to chemists. Is sufficient effort being devoted to the application of the knowledge we already possess? What should be the priorities? How can we ensure that the same concerted effort is made to use that knowledge for the peace and contentment of the world as made it such a potent factor in the war? That is the thought I would leave with you at the beginning of our second century.

The Development of Electrochemical Theories of the Course of Reactions of Carbon Compounds.

THE EIGHTEENTH FARADAY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON
JULY 16TH, 1947.

By SIR ROBERT ROBINSON, M.A., D.Sc., LL.D., P.R.S.

THERE are many tributaries to the river of scientific progress, and their contribution to the broad stream persists in spite of inevitable loss of individual form.

So, the modern theories of molecular structure and chemical reactions which flourish in the domain of physical chemistry, thermodynamics, and wave mechanics, are derived from many sources. It is my intention to speak of only one of these, namely that provided by the generalisations of their experience which organic chemists have been able to make in terms of the electronic conception of valency.

That these generalisations were a real forward step cannot be doubted, but the form in which they were expressed has naturally been altered in accordance with the successive advances in our knowledge of the fundamentals of chemical kinetics and atomic and molecular theory.

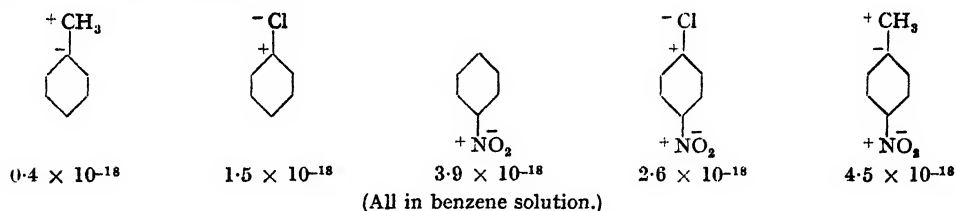
The identity of the ideas has not yet been lost, however, and the qualitative approach still affords a valuable framework for the elaboration of detail by means of the more searching methods of analysis which are now available. But the section of the subject that I have indicated is small only in relation to the whole; it is very complex in itself and is the outcome of developments in varied fields of work. It will be convenient to follow the thread suggested by the lecturer's contacts with the topic and by precedent and parallel investigations, but it is certain that, by a change of emphasis, many different lectures could be delivered under the same title.

After the discovery of the electron by Sir Joseph Thomson and the successive stages in the formulation of the electrical theory of the constitution of matter, the conceptions of the nature of chemical affinity and valency bonds were gradually adjusted, and attempts were made to explain the chemical properties of molecules as assemblages of electrons and positively charged nuclei. Some kind of electronic theory of valency became almost axiomatic, but, as the development showed, there was ample scope for divergent views of details of structure, of the nature of the forces involved, and of the interpretation of physical and chemical properties. The idea of covalency, the sharing of electrons by two nuclei, was adumbrated by Ramsay in 1908. Thomson and Stark developed more detailed theories, and were among the first to attack problems of organic chemistry on an electronic basis.

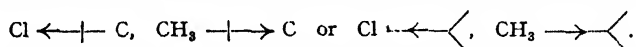
The speculative elaborations of Stark ("Die Elektrizität im chemischen Atom", Leipzig, 1915), who also advanced electronic explanations of optical properties, have not survived in their original form. Many of his suggestions may, however, be traced in later theories. A second epoch may be roughly defined as that of Kossel (*Z. Physik*, 1920, **1**, 395) and of Lewis (*J. Amer. Chem. Soc.*, 1916, **38**, 762; "Valence and the Structure of Atoms and Molecules", Amer. Chem. Monograph, 1923), characterised, at least in its earlier phases, by somewhat rigid conventions in regard to the chemical bond, and by great advances in our knowledge of the relation of structure to physical properties. In the third and present period the applications of wave mechanics are yielding more precise information in regard to the distribution of electrons in the molecules. In certain cases that distribution can even be determined from experimental observations of the reflexion of X-rays by crystals. These matters lie outside the purview of the present lecture. Indeed, the symbols which we still employ are largely independent of stereo-electronic considerations. The exceptions are those used for the polar molecules, to the study of which Debye has made such outstanding contributions, and for the ions, that is to say the bound and free ions. At every stage of the electrochemical theory these are our trusted guides.

Langmuir pointed out that trimethylamine oxide, formed from electrically neutral NMe_3 and an uncharged oxygen atom, must be $\text{Me}_3\text{N}^+\text{O}^-$ by the arithmetic of the electrons, and Sidgwick extended the idea to include many compounds containing the co-ordinate link $\text{A} \xrightarrow{(+)} \text{B} \xleftarrow{(-)}$ ("The Electronic Theory of Valency," Oxford, 1927). The existence of these dipolar groups has been fully established by experiment and has been correlated with a range of physical and chemical properties. The knowledge has been used to confirm the assumed orientation

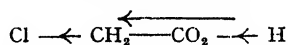
of electrostatic doublets produced by simple substitutions. For example, on theoretical grounds Thomson showed that such a doublet should be present in the group C-Cl, and this is confirmed by the fact that methyl chloride has an electric moment, 1.97×10^{-18} e.s.u., in the gaseous state. The direction of the moment is shown by a comparison of the dipole moments (e.s.u.) of chlorobenzene, nitrobenzene, and *p*-chloronitrobenzene, because NO_2 , a dipole like an amine oxide, must be N^+O_2^- .



It is clear that the separate dipole moments due to C-Cl and C- NO_2 are in opposite directions in the molecule, or in other words they are in the same direction with respect to the nucleus. Substitution of methyl for hydrogen in the aromatic nucleus produces a small dipole moment in the opposite sense. We denote these displacements by the symbols :



Both Thomson and Lewis assumed that such doublets would exert an effective field, either directly or by induction through a chain of atoms, and gave in illustration the greater strength of the chloroacetic acids as compared with acetic acid. The operation of the electrical field on the carboxyl group will obviously enhance the stability of the anion produced by electrolytic dissociation. As expressed by Lowry the sheath of electrons moves towards the chlorine atom and thus bares the nuclei of the oxygen atoms, enhancing their repulsion on the attached proton.



Lewis pointed out that the effect diminishes as the chlorine atom is removed from the carboxyl. Thus α -chloropropionic acid is about as strong as chloroacetic acid, but β -chloropropionic acid is much weaker. γ -Chlorobutyric acid is still weaker, and the effect is hardly discernible in δ -chlorovaleric acid.

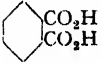
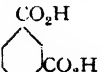
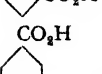
Ionisation constants of aliphatic acids.

	<i>K</i> .
$\text{CH}_3 \cdot \text{CO}_2\text{H}$	2.1×10^{-5}
(Br) $\text{CH}_2\text{Cl} \cdot \text{CO}_2\text{H}$	1.55×10^{-5} (Br, 1.38×10^{-5})
$\text{CHCl}_2 \cdot \text{CO}_2\text{H}$	5×10^{-5}
$\text{CCl}_3 \cdot \text{CO}_2\text{H}$	2×10^{-1} (?)
$\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	1.4×10^{-5}
(Br) $\text{CH}_2 \cdot \text{CHCl} \cdot \text{CO}_2\text{H}$	1.47×10^{-5} (Br, 1.08×10^{-5})
(Br) $\text{CH}_2 \cdot \text{Cl} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	8.59×10^{-5} (Br, 9.8×10^{-5})
$\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	1.6×10^{-5}
(Br) $\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHCl} \cdot \text{CO}_2\text{H}$	1.39×10^{-5} (Br, 1.06×10^{-5})
$\text{CH}_2 \cdot \text{CHCl} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	8.94×10^{-5}
(Br) $\text{CH}_2 \cdot \text{Cl} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	3×10^{-5} (Br, 2.6×10^{-5})
$\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	$1.5 - 1.6 \times 10^{-5}$
(Br) $\text{CH}_2 \cdot \text{Cl} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$	2.04×10^{-5} (Br, 1.9×10^{-5})
$\text{C}(\text{CH}_3)_3 \cdot \text{CO}_2\text{H}$	1.5×10^{-5}
$\text{CH}(\text{CH}_3)_2 \cdot \text{CO}_2\text{H}$	9.8×10^{-6}
$\text{CH}_2 \cdot [\text{CH}_2]_4 \cdot \text{CO}_2\text{H}$	1.45×10^{-5}
$\text{CH}_2 \cdot [\text{CH}_2]_5 \cdot \text{CO}_2\text{H}$	1.46×10^{-5}
$\text{CH}_2 \cdot [\text{CH}_2]_6 \cdot \text{CO}_2\text{H}$	1.44×10^{-5}
$\text{CH}_2 \cdot [\text{CH}_2]_7 \cdot \text{CO}_2\text{H}$	1.44×10^{-5}

Dippy and R. H. Lewis (*J.*, 1937, 1008) noted an almost linear relation between the dipole moments and the electrolytic dissociation constants of a number of acids.

In the series of the dibasic acids we can study the effect of one carboxyl on the strength of another at varying distances.

Ionisation constants of dibasic acids.

	K_1	K_2
$\text{CO}_2\text{H}\cdot\text{CO}_2\text{H}$	7×10^{-2}	$3\text{--}7 \times 10^{-5}$
$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$	$1\cdot46\text{--}1\cdot63 \times 10^{-3}$	$2\cdot1(1\cdot4) \times 10^{-6}$
$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$	$8\cdot1 \times 10^{-5}$	$3\cdot7 \times 10^{-6}$
$\text{CO}_2\text{H}\cdot[\text{CH}_2]_3\cdot\text{CO}_2\text{H}$	$4\cdot7(6\cdot9) \times 10^{-5}$	$2\cdot9 \times 10^{-6}$
$\text{CO}_2\text{H}\cdot[\text{CH}_2]_4\cdot\text{CO}_2\text{H}$	$3\cdot7 \times 10^{-5}$	$2\cdot4 \times 10^{-6}$
$\text{CO}_2\text{H}\cdot[\text{CH}_2]_5\cdot\text{CO}_2\text{H}$	$3\cdot23 \times 10^{-5}$	$4\cdot4 \times 10^{-6}$
$\text{CO}_2\text{H}\cdot[\text{CH}_2]_6\cdot\text{CO}_2\text{H}$	$2\cdot5 \times 10^{-5}$	$2\cdot4 \times 10^{-6}$
$\text{CO}_2\text{H}\cdot[\text{CH}_2]_7\cdot\text{CO}_2\text{H}$	$2\cdot7 \times 10^{-5}$	$2\cdot5 \times 10^{-6}$
	$1\cdot3 \times 10^{-3}$	$3\cdot4\text{--}5\cdot8 \times 10^{-6}$
	$2\cdot9 \times 10^{-4}$	$2\cdot4 \times 10^{-5}$
	$1\cdot5 \times 10^{-4}$	
$\text{Ph}\cdot\text{CO}_2\text{H}$	$6\cdot5 \times 10^{-5}$	

It is apparent that $\cdot\text{CO}_2\text{H}$ behaves like $\text{C}\cdot\text{Cl}$. As Thomson's electrostatic argument suggests,* it must be represented as $\overset{\delta+}{\text{C}}\overset{\delta-}{\text{O}}_2\text{H}$, and it is electron-attracting. But after dissociation the group becomes $\text{--}\bar{\text{CO}}_2$; there is now no question of a dipole,† but only of a negative charge which should repel electrons and conversely hold protons even at a distant point. The second dissociation constants clearly show that this anticipated reversal of the effect occurs.

The values quoted for K_2 are not always strictly comparable with one another, or with those for K_1 . The second dissociation constants were in some cases determined at 100° by the method of inversion of sucrose (cf. Smith, *Z. physikal. Chem.*, 1898, 25, 220). It may be noted that E. Q. Adams (*J. Amer. Chem. Soc.*, 1916, 38, 1503) has shown that if the first dissociation had no effect on the second, K_2 should be one-fourth of K_1 . When the carboxyl groups are far removed from one another, this relation was found to hold approximately (cf. Chandler, *J. Amer. Chem. Soc.*, 1908, 30, 694).

The case of isomeric acids differing in stereochemical configuration is particularly convincing.

Ionisation constants of stereoisomeric dibasic acids.

	K_1	K_2
$\begin{array}{c} \text{CH}\cdot\text{CO}_2\text{H} \\ \\ \text{CO}_2\text{H}\cdot\text{CH} \end{array}$	$9\cdot8 \times 10^{-4}$	$2\cdot7 \times 10^{-5}$
$\begin{array}{c} \text{CH}\cdot\text{CO}_2\text{H} \\ \\ \text{CH}\cdot\text{CO}_2\text{H} \end{array}$	$1\cdot3 \times 10^{-2}$	$2(2\cdot6) \times 10^{-7}$
$\begin{array}{c} \text{CMe}\cdot\text{CO}_2\text{H} \\ \\ \text{CO}_2\text{H}\cdot\text{CH} \end{array}$	$8\cdot5 \times 10^{-4}$	9×10^{-6}
$\begin{array}{c} \text{CMe}\cdot\text{CO}_2\text{H} \\ \\ \text{CH}\cdot\text{CO}_2\text{H} \end{array}$	$3\cdot8 \times 10^{-3}$	$2\cdot4 \times 10^{-7} (100^\circ)$

The *cis*-acids are much the stronger as monobasic acids but they are far weaker in the second ionisation step. The ratio of K_1 to K_2 for fumaric acid is about 36 and for maleic

* However, in opening a discussion on these topics in 1923 (Faraday Society) Sir Joseph Thomson classed Cl , OH , NH_2 , and CH_3 together ($\overset{+}{\text{C}}\text{--}\bar{\text{Cl}}$) and distinguished their effect from that of CN and NO_2 ($\bar{\text{C}}\text{--}\overset{+}{\text{CN}}$). This view appears to have been based on some kind of alternation and disregards the inductive transmission of the field of a doublet. Thus $\bar{\text{C}}\text{N}^+$ distributes a positive field over the atoms to which it is attached and, of the groups mentioned, $\bar{\text{CH}}_3$ is the only one that produces a negative field.

† This is not true of the sulphonic ion, SO_3^- . Thus K_2 for *p*-sulphobenzoic acid is $1\cdot4 \times 10^{-4}$ ($>K$ for $\text{Ph}\cdot\text{CO}_2\text{H}$, $6\cdot5 \times 10^{-5}$). There is other evidence that SO_3^- distributes a positive electric field over an attached group, and this is clearly due to its constitution $\text{--}\overset{+}{\text{S}}\overset{+}{\text{O}}_3^-$, the nearer double positive charge being more effective than the more remote triple negative charge.

acid about 50,000. Attention should be paid to the order of the phenomena only, as, apart from the experimental difficulties, the interpretation is complicated by the possibility of differences of solvation of the acids and their ions.

Many of these facts were established by the work of Walker, Ostwald, and Bone, Sprankling, and Sudborough fifty to sixty years ago, and Ostwald gave the acceptable explanation of them in general terms (*Z. physikal. Chem.*, 1889, **3**, 177).

The whole problem of the strengths of acids and bases (where the effects are naturally reversed) can be satisfactorily treated along similar lines, but, as Flürscheim was the first to show (*J.*, 1909, **95**, 718; 1910, **97**, 84), steric hindrance must be taken into account in many cases, for example in *o*-substituted benzene derivatives. We may regard the dissociation constant of a carboxylic acid as a measure of the electrical field over the dissociating group, provided that approach of solvent molecules is not hindered by steric conditions.

I have dwelt at some length on this clear case because of its historical importance and in order to place in juxtaposition with it, experimental results from which it can be seen that exactly analogous phenomena control the nitration of certain benzene derivatives in the *o*-, *p*-, or *m*-positions with respect to a substituent. With the acids we have an ionic equilibrium and the effect of an electric field is not surprising. But in the nitration case we have an effectively irreversible process and no obviously ionic reaction.

The work of Vorländer showed that the direct attachment of an 'onium group to the benzene nucleus gives substances that nitrate exclusively in the *m*-position (*Ber.*, 1919, **52**, 262, 274; Vorländer and Siebert, *ibid.*, p. 283). This may be compared with the *m*-nitration of nitrobenzene (benzoic acid, benzenesulphonic acid, etc.):



The "'onium" atom need not be nitrogen but may be sulphur, selenium, phosphorus, arsenic, antimony, bismuth, lead, or even iodine [Vorländer and Büchner, *Ber.*, 1925, **58**, 1898 (I); Vorländer and Schroedter, *ibid.*, p. 1900 (Bi, Pb); Michaelis and Soden, *Annalen*, 1885, **229**, 324 (a P compound not quite analogous); Ingold, Shaw, and Wilson, *J.*, 1928, 1280 (P, As, Sb); Baker and Moffitt, *J.*, 1930, 1722 (S, Se)].

The interpretation given by Vorländer laid emphasis on the direct union of the "'onium" atom to the nucleus and is no longer considered valid.

In 1902 Schultz and Bosch (*Ber.*, 1902, **35**, 1292) stated that phenylbenzylethylamine nitrated in the *m*-position in the benzyl group, and Noelting and Kregec (Bull. Soc. chim., 1916, **19**, 355) recorded the *m*-nitration of benzyldiethylamine, both in strongly acid solution. The significance of these isolated observations was not quickly recognised, mainly because there was no orientation theory that was generally considered satisfactory. A few years later interest was awakened and an active discussion arose in this country on the question of the actual substance that nitrates in the *m*-position. Was it the base or the salt? This was settled in favour of the latter view by Ing and the lecturer (*J.*, 1926, 1655) who found that benzyltrimethylammonium nitrate furnished nearly 90% of the *m*-nitro-derivative. In this quaternary salt the existence of free base is naturally impossible. The paper was entitled "The orienting influence of free and bound ionic charges", and the *m*-nitration in this and other cases was attributed to an electrical field produced by the cation over the molecule. The result was of great importance because it demonstrated that the charged centre need not be directly connected to the nucleus.

In a footnote it was stated that the work would be extended to β -phenylethyltrimethylammonium nitrate and γ -phenylpropyltrimethylammonium nitrate in order to determine the influence of the length of chain separating the charged centre and the nucleus. Even in the former case the nitration was chiefly in the *p*-position. Quantitative details of these and other examples were later provided by the extensive work of Ingold and his school.

It was found that, when a cationic charge is separated by a methylene group from the benzene ring, the nature of the 'onium atom is significant. Other things being equal the heavier atoms are the less effective, possibly because the distance from the aromatic nucleus is increased by their larger radius and the nuclear positive charge is more diffuse. Examination of the results demonstrates conclusively that the proportion of *m*-nitration is dependent on the intensity of the positive electric field over the nucleus.

m-Nitration of 'Onium Salts, Ph·R.

R = CH₃·NMe₃⁺, 88%;¹ R = CH₃·CH₂·NMe₃⁺, 19%;² R = CH₃·CH₂·CH₂·NMe₃⁺, about 5%;³ R = PMe₃⁺, 100%;⁴ R = CH₃·PMe₃⁺, 10%;⁴ R = AsMe₃⁺, 98%;⁴ R = CH₃·AsMe₃⁺, 3·4%;⁴ R = SbMe₃, 86%;⁴ R = SMe₂⁺, 100%;⁵ R = CH₃·SMe₂⁺, 52%;⁵ 2-phenylbenzopyrylium salts⁶ and 2-phenylquinoline metho-salts,⁷ only *m*-nitro-derivatives were isolated, and in high yield.

¹ Ing and Robinson, *loc. cit.*; Goss, Ingold, and Wilson, *J.*, 1926, 2240. ² Goss, Hanhart, and Ingold, *J.*, 1927, 250. ³ Ingold and Wilson, *J.*, 1927, 810. ⁴ Goss, Ingold, and Wilson, *loc. cit.* ⁵ Baker and Moffit, *loc. cit.*; Pollard and Robinson, *J.*, 1930, 1765, found Ph·CH₂·SEt₃⁺, *m*-nitration, 28%. This fall, as compared with the benzyldimethylsulphonium salt, is probably due to reduction of the positive 'onium field of sulphur by a negative field due to the methyl groups. ⁶ Le Fèvre, *J.*, 1929, 2771. ⁷ Le Fèvre, *J.*, 1930, 2236.

Flürschheim and Holmes (*J.*, 1926, 1562) and Pollard and Robinson (*J.*, 1927, 2770) found cases in which the electrostriction of the cations by added salts diminished the percentage of *m*-nitration. Thus benzyldiethylamine in an excess of sulphuric acid gives 53·5% of the *m*-derivative. When ammonium sulphate was added the proportion fell to the region of 33%. The nitration of benzylpiperidine in nitric acid (*d* 1·5) gives about 70% of the *m*-nitro-base, and addition of trimethylammonium nitrate or rubidium nitrate, salts which are soluble in nitric acid, caused progressive reduction as more of the salts was added, until only about 20% of the *m*-derivative was produced. It was suggested that the accessibility of, for example, a sulphonium cation to electrostriction may be a part of the cause of the less intense field (as compared with a corresponding ammonium cation) that it exerts over the aromatic nucleus.

It was pointed out long ago by Holleman ("Die direkte Einführung von Substituenten in den Benzolkern", 1910, p. 469) that predominant *op*-substitution occurs at a higher rate and under milder conditions than predominant *m*-substitution.

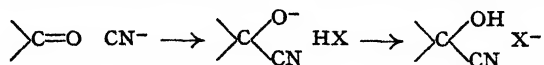
This is easy to understand in the series which has been discussed because the recent work of Bennett and Ingold and their collaborators has indicated that the effective nitrating agent, at least in sulphuric acid solution, is the nitroxyl ion, NO₂⁺. Obviously this will be repelled by a positive field and will enter the molecule the more easily the less intense the field. The relation indicated by this example is general and is often diagnostic of an ionic type of reaction. In regard to the actual rates in different cases Wibaut (*Rec. Trav. chim.*, 1915, 84, 241) found the order C₆H₅·CH₃ > C₆H₆ > C₆H₅Cl > C₆H₅Br in acetic anhydride solution. Using the method of competitive nitration, Ingold and Shaw (*J.*, 1927, 2918) calculated from their results that each *o*- and *p*-position in toluene is roughly thirty times as reactive as in benzene, and each *m*-position about twice as active as one of the positions in benzene. The ratio R_{C₆H₅R}/R_{C₆H₆} was found to be R = I, > 1; R = Br, 0·2; R = Cl, 0·01; R = F, 0·002. Ingold, Lapworth, Rothstein, and Ward (*J.*, 1931, 1959) working under somewhat different conditions increased the figures for toluene and found that one of the *m*-positions is about three times as active as one position in benzene. Although the assumptions made in the calculations hold only approximately and may be arguable, the general trend of the phenomena was established. It is in agreement with the theory outlined that the *m*-position of toluene should be activated (see below).

Excluding the cases (conjugated systems) considered later, all the data on benzene substitution can be shown to be in harmony with these principles. If we withdraw electrons from the nucleus as by substitution of halogens, nitro-groups, carboxyl groups, etc., for hydrogen in the side-chain we augment *m*-nitration. Introduction of methyl groups into the side-chain augments *op*-nitrations. Nitration has been studied very extensively but enough is known of sulphonation and halogenation to demonstrate that the orientation in these processes follows the same general lines. In order to be able to discuss why *m*-nitration occurs under the influence of a positive electric field, it is necessary to study other aspects—the reagents, and the behaviour of unsaturated systems.

The Classification of Reagents as Anionoid and Cationoid.—These terms introduced by Lapworth (*Manchester Phil. Soc.*, 1925; cf. *Nature*, 1925, 115, 625) implied that certain electrically neutral molecules exhibit reactions of ionic type. Thus the hydroxyl ion combines with a proton to form water, and when water combines with a proton to form the solvated hydrogen ion, the process is evidently analogous. Hence the water molecule is said to be anionoid or to be an anionoid complex. The terms are equivalent to electron-donor and electron-acceptor and also to Ingold's expressions nucleophilic and electrophilic, respectively.

When a neutral molecule is attacked by an ion, the site of a cationoid or anionoid position is easily located, and it was just such a case that led Lapworth to develop his system of incipient

alternate polarities. The reference is to the formation of cyanohydrins which were conclusively demonstrated, qualitatively and by kinetic studies, to result from the attack of cyanide ion on a carbonyl group. The resulting complex ion then takes a proton from a suitable source, such as water or an alcohol, or even from a molecule of hydrocyanic acid:



Thus pure hydrocyanic acid does not combine with aldehydes or ketones, but the alkali from a glass vessel is sufficient to start the succession of processes.

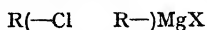
Hence the carbon of the carbonyl group is said to be "cationoid". All the characteristic reactions of carbonyl compounds conform to this view. By analogy we also class many similar groups as cationoid, for they evidently undergo the same type of reactions. These include carboxyl and especially the carboxylic ester group, the cyano- of nitriles, nitrosyl and nitroxyl groups.

The cationoid character of the carbon of -CO- could be deduced theoretically from the fact that oxygen has a greater affinity for the negative charge than carbon, but there is no such guide in the case of the carbon-carbon double bond, and a conclusion had to be based on what was already known of the characteristic behaviour of olefins. This knowledge was sufficient for the purpose but it was eked out by specifically designed tests, among which may be mentioned Gilman's demonstration that olefins are inert towards organometallic compounds.

Consideration of the reactions of the olefins showed that in general and under ordinary conditions, they are easily attacked by cations and cationoid reagents but are relatively inert to anions and anionoid reagents. They were therefore regarded as anionoid. But this only means that their additive reactions are *usually initiated* by electron-donation to reagents; there must always be a subsequent process in the course of which the second carbon of the system evinces cationoid character.

In the formation of cyanohydrins it is clear that the group $>\text{C}=\text{O}$ becomes $>\text{C}^+\text{O}^-$, and any part of this full displacement of an electron pair is conveniently represented by the symbols $\text{>}\overset{+}{\text{C}}=\text{O}$ or $\text{>}\overset{\delta+}{\text{C}}=\overset{\delta-}{\text{O}}$. Similarly any part of the full displacement of a pair of electrons in an olefin can be represented as $\text{>}\overset{+}{\text{C}}=\overset{-}{\text{C}}<$. The difference is that whereas the carbonyl is cationoid at (a) the olefin is anionoid at (b). There is complete analogy between the reactions of the olefins and those of the aromatic compounds which tend to retain their type, and therefore benzene, and all similar substances, are also classed as anionoid.

Saturated carbon, midway between lithium and fluorine, has little or no intrinsic tendency to be either anionoid or cationoid. Therefore alkyl groups exhibit either behaviour in accordance with the electrochemical character of the group or atom to which they are united. Thus a chlorine atom holds the covalency electrons tenaciously and tends to separate as an ion. An attached alkyl group is consequently cationoid. But metals easily relinquish electrons and hence the alkyls of organometallic compounds are anionoid.



The annexed table requires little further explanation and can, of course, be greatly extended.

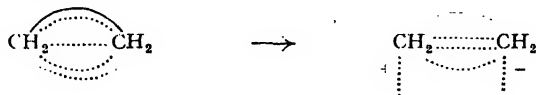
Anionoid.	Cationoid.
<i>Nucleophilic.</i>	<i>Electrophilic.</i>
<i>Electron-donating.</i>	<i>Electron-accepting.</i>
Active anions (OH^- , CN^- , etc.).	Active cations (H_3^+O , ϕN_3^+).
Anionoid complexes with unshared electrons (R_3N , ROH , etc.).	Atoms with incomplete electron configurations (neutral O; Co, Pt, etc.; BF_3 , AlCl_3).
Reducing agents ($\text{Fe}^{++} \longrightarrow \text{Fe}^{+++}$).	Oxidizing agents [$\text{Fe}(\text{CN})_6^{4-} \longrightarrow \text{Fe}(\text{CN})_6^{3-}$].
Metals as electron sources.	Halogens, nitric acid (in nitration), sulphuric acid (in sulphonations).
R in R_3Zn , RMgX , etc.	R in RCl , R_2SO_4 , NR^+ , etc.
$\text{:C}\equiv\text{C:}$, C_6H_6 , etc.	$\text{:C}\equiv\text{O}$ (at carbon), etc.
Free radicals.	Free radicals.

In all the classes the various representatives can be arranged in order of reactivity, and one general principle is that unshared electrons are better donors, the smaller their number.

to be the case, and it would also react with anionoid reagents. But once the electron donation from an ethylene molecule has commenced, strain is relieved, and the process can be continued. Hence the full displacement is assumed to occur only in the course of the reaction. Again the process is not one of interaction with halogen cations but with halogen molecules, because the concentration of the former, if they are present at all, must be extremely low and the kinetics would be inexplicable. Finally the concentration of hydroxyl ions in the strongly acid solution is certainly exiguous.

The Conjugated Systems.—(1) *Polyenoid.* In 1911 Hugo Kauffmann ("Die Valenz Lehre", Enke, Stuttgart) developed a theory of partial and distributed valency which he applied with success to the problem of auxochromes and to the constitutions of benzene and the triphenyl-methane dyes. He appears, however, to have regarded chemical affinity as a special kind of force and speaks of the valence fields becoming electric fields, if electrons are interposed. In other respects too, and particularly in the development, Kauffmann's views differed from those that the lecturer developed from 1916 (*J.*, 1916, 109, 1032, 1041; 1917, 111, 959; 1918, 113, 643; *Mem. Manchester Phil. Soc.*, 1920, 64, No. 4) and which were translated in 1922 into definite electronic symbols (Kermack and Robinson, *J.*, 1922, 121, 427).

It was postulated that a valency bond could be subdivided, to an unknown but large extent, and it was further assumed that molecules are polarised by such partial division of the bonds. The polarised complexes enter into reactions. Thus taking four subdivisions of a bond, for convenience only, the activation of ethylene was represented as

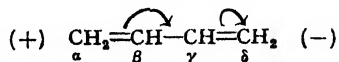


With this polarised form the reaction, say addition of bromine, could be initiated and it was supposed to be completed in the course of the process by further division and rearrangement of the valencies. This view differed from that of Thiele in that the partial valencies were derived from the normal valencies and were not additional to them. The schemes for butadiene illustrate this contrast of which the most significant aspect is the assumption of polarisation:



Here the signs on C^β and C^γ represented the polarity of the partial valencies from which the central partial bond was derived. It was an error to retain these signs after the part bond was formed, but the convention gave the right results in more complex systems.

Although these ideas were based from the commencement on the electronic theory of valency, use was made for some years of the partial polarised valency expressions. It was realised that the partial valencies labelled (−) represent available electrons, or part of an electron, and that those labelled (+) represent corresponding electron defect. Therefore the equivalent electronic symbol for polarised butadiene is:



This implies that a certain electron value, possibly quite a small fraction of one electron, becomes free on C^δ and that the resulting electron defect on C^γ is made up by the transfer of a corresponding electron fraction from the $C^{\alpha\beta}$ bond to $C^{\beta\gamma}$, and that this produces a corresponding electron defect on C^α . A very important feature of this representation is that, apart from the inevitable electron defect on one carbon atom, the number of quantised electrons in the configurations of the carbon atoms is unchanged. The mechanism of addition to this system will then be precisely analogous to that already discussed for ethylene. It will be noticed that the process transfers electron defect from C^γ to C^α but this event does not *always* occur. The left-hand arrow need not come into operation and, as experience shows, we may observe $\gamma\delta$ (or $\alpha\beta$) additions. It is obvious, and was clearly stated, that a double bond can transmit *any* effect of electron accession or recession and one or more double bonds can there-

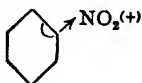
fore be interpolated in any system AB such that the quality of reactivity exhibited is due to a displacement of electrons from A to B, directly, or through an external circuit.

Much later Fuson (*Chem. Reviews*, 1935, 16, 1) called this the "Principle of Vinylogy". It is a theoretical potentiality which is not always realised in practice. The effects may be greatly damped, and there are special exceptions such as $R\cdot Cl$, $R\cdot CH=CH\cdot Cl$, the cause of which is apparent.

The polarised complexes of which butadiene is the type are called *polyenoid*. They include benzene and other aromatic hydrocarbons.

We are now in a position to consider why an electric field over the benzene nucleus should produce *op*-substitution or *m*-substitution according to its direction and intensity (Allan, Oxford, Robinson, and Smith, J., 1926, 409).

The reagent in nitration is cationoid; * it is looking for electrons. Therefore the first stage of the nitration of benzene could be represented as :

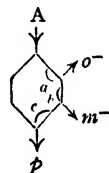


The second stage is the removal of the proton at the point attacked. That is also important but need not enter into the present discussion.

Now suppose we have a group (A) which promotes electron accession to the nucleus and a



general drift or repulsion of electrons as shown in the figure. Its effect will be a maximum at the carbon atom to which it is attached and less work will be needed to effect the polarisation (a) than (b) or (c) :



Thus *o*-substitution can be expected. If the reagent approaches the *m*-position substitution may occur through the independent operation of (b) but it will be far less facile. But if the reagent approaches the *p*-position and enters into tentative union with it, the defect on the *m*-carbon can at once be made up by a conjugative process (d) which will be favoured by the same circumstances that helped (a) :



Thus the push from (A) promotes *o*-substitution directly and *p*-substitution by conjugation. It is important to note that the process (b) cannot be assisted in a similar fashion, because in the expression



the number of electrons in the configuration of the *m*-carbon is increased.

We have seen that methyl is an (A) group; the percentage of *m*-nitration of toluene is 4 and the ratio of *o*- to *p*-nitration is about 3 : 2 (*o*-, 59% ; *p*-, 37%).

* It is not certain that NO_2^+ is the sole nitrating agent; electrically neutral cationoid complexes are probably operative under appropriate conditions.

A group (B) which attracts electrons is equivalent so far as the field effect is concerned to an imaginary (A) group at the *p*-position:

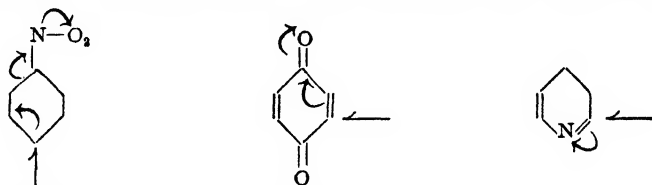


Hence by the argument already given we anticipate *op*-substitution with respect to (A). That is, *m*-substitution with respect to (B), or displacement of that group by the substituent. The latter phenomenon is often encountered.

Naturally this use of the imaginary (A) group must not be pressed too far. The group (B) is real and by its positive electric field it renders all the nuclear electrons less available and reduces the ease and velocity of the substitution reaction.

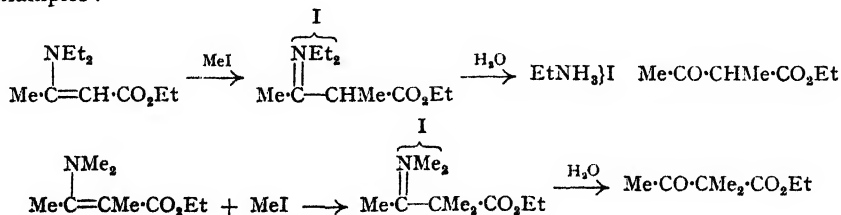
(2) *Catio-enoid*. The cationoid reactivity of the carbon of a carbonyl group has been attributed to the electronic displacement >C=O . This can be conjugated with a double bond and thereby the quality of reactivity of a carbonyl is transferred to a carbon of the ethenoid system C=C-C=O . It is another example of the $\alpha\gamma$ rule. Thus a cyanidion attacks the γ -carbon (usually denoted as β) in an unsaturated ketone. Consideration of these and similar cases led Lapworth (1920) to formulate his theory of alternate polarities expressed: $\text{C}^+=\text{C}^--\text{C}^+=\text{O}$. In this way he merely indicated the polarities which the various atoms seemed to display at the moment of reaction. The device led to some useful and interesting results but it was certainly taken too literally, and Lapworth's clearly stated reservations were often overlooked by other workers. Later (1922) he adopted a view similar to that suggested by the lecturer, but this was presented in a very general form which was somewhat difficult to assimilate.

In the aromatic series, catio-enoid systems may lie outside the nucleus, partly in the nucleus, or wholly in the nucleus. They give rise to typical reactions with *anionoid* reagents:

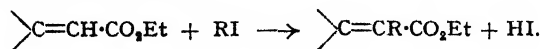


Examples are the hydrolysis of nitrosodimethylaniline and 1-chloro-2:4-dinitrobenzene, the amination and hydroxylation of nitrobenzene, quinones, and pyridine, etc. etc.

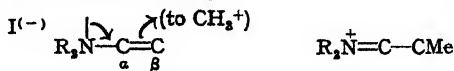
(3) *Hetero-enoid*. H. Decker (Decker and Klauser, *Ber.*, 1904, **37**, 523; Decker, *Ber.*, 1905, **38**, 2893) suggested that tervalent nitrogen could be conjugated with a double bond, and employed the Thiele symbol: $\text{C}=\text{C}-\text{N}^{\cdot}$. The experimental basis of the divided addition concerned only the action of acids and therefore the mobile proton. The lecturer (*J.*, 1916, **109**, 1038) showed that alkyl groups could be used to mark the position of combination as in the examples:



This latter case excludes the hypothesis



The basic nitrogen attached to the double bond has transferred, to unsaturated carbon, its own power of combining with a cationoid methyl group. The facts were established in the partial valency period and expressed in terms of that hypothesis. The electronic translation (1922) is much simpler and more convincing.



The unshared electrons (lone pair) of the nitrogen atom are used to increase the covalency with the nearest unsaturated carbon C α . This must release electrons of the double bond to C β which can thus bind the methyl group. At the same time the nitrogen acquires a positive charge to balance the iodion, for it started with unshared electrons which became shared in the process.

It is quite clear that this system must be definitely anionoid or electron donating. For though olefins are anionoid the tervalent nitrogen is far more strongly so, and here the nitrogen atom endows the unsaturated group with something of its own quality. Furthermore this type of conjugation is possible if the nitrogen atom is replaced by any atom which carries unshared electrons, and the order of activation will be that of the proton-affinity (or basic strength) of the hetero-atom: the greater that affinity the more reactive will be the anionoid carbon. Thus $\text{N}^- > \text{O}^- > \text{N} > \text{O} > \text{I} > \text{Cl}$ to mention a few of the possibilities. The C-alkylation of the sodio-derivative of ethyl acetoacetate which is derived from the enolic form, is seen to be analogous to the C-alkylation of the β -aminocrotonic esters. The most important examples are in the aromatic series, *e.g.*, the phenoxide ion, the aromatic amines, phenols and their ethers, halogenobenzenes. All the characteristic nuclear reactions of phenols and amines, *e.g.*, bromination, nitration, condensation with carbonyl compounds, etc., are with cationoid reagents, and all occur exclusively in the *op*-position. The conjugations



provide a much more definite mechanism of activation than that previously considered, and they take precedence over other effects. It has been suggested by J. W. Baker and Nathan (*J.*, 1935, 1845) that a methyl group can release electrons in a somewhat similar fashion:



The relation of this suggestion to the use of unshared electrons in the systems under discussion is not yet clear.

The case of chlorobenzene is very interesting because its nitration, for example, is far less facile than that of benzene itself. This was to be expected, for chlorine is known to be an electron-attracting group as we have already seen:



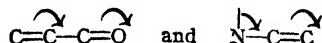
All the electrons of the nucleus are less available than they are in benzene. But even at this low level of reactivity the conjugative process determines where the donor electrons are to be found (see below, mesomerism).

Other important hetero-enoid systems are recognised in such substances as pyrrole, and account for the correspondence of its reaction types with those of phenol and dimethylaniline:



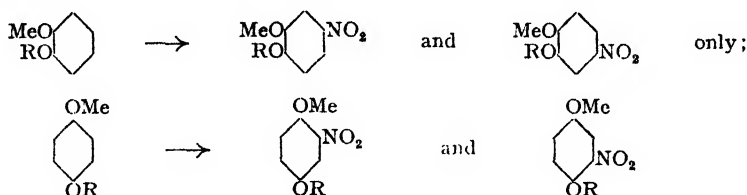
The α -positions are like the p -position in aniline, whereas the β -positions resemble the o -positions in aniline. They are all reactive as shown by the formation of tribromoaniline on the one hand and tetraiodopyrrole on the other.

The recognition of two kinds of conjugated changes of covalency with simultaneous increase or decrease of the unshared electrons of atoms such as oxygen or nitrogen as in

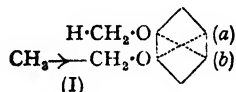


must be regarded as one of the milestones on the road we have travelled.

An Example of the Interaction of the Conjugated Polarisation and General Electric Effects.—A very important aspect of the lecturer's views was experimentally illustrated by a carefully selected case (three preceding papers were discussed by Allan, Oxford, Robinson, and Smith, *loc. cit.*; Lea and Robinson, *J.*, 1926, 411; Oxford and Robinson, *J.*, 1927, 2239; Fawcett and Robinson, *J.*, 1927, 2415; Clarke, Robinson, and Smith, *J.*, 1927, 2647; Smith, *J.*, 1931, 251). This was the mono-nitration of alkyl ethers of catechol and quinol (OMe, OR) which proceeds quantitatively. The proportions of the products can be determined accurately by thermal analysis.

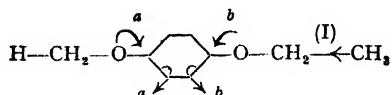


If we consider the case of the ethyl ether of guaiacol, there are two hetero-enoid systems directing p -substitutions as indicated by the dotted lines :



The oxygen of the methoxyl group directs the substituent to (b), that of the ethoxyl group to (a). In the ethoxyl group a hydrogen of the methoxyl group is replaced by methyl, and this, as we know from strengths of acids and bases and from the dipole moment of toluene, will repel electrons relative to the effect of hydrogen. Hence the system terminating in (a) should be reinforced and the directive power of ethoxyl should exceed that of methoxyl; which is actually found to be the case. Taking MeO, 100 we find EtO, 135. But on increasing the size of R in OR, the directive power rises to a maximum and then falls: Pr^oO, 150; Pr^oO, 128; *n*-BuO, 123.

The effect (I) (inductive or general) is evidently also exerted on the oxygen of the methoxyl as the stereochemical conditions suggest that it should be, and the distributed direct effect partly neutralises that exerted through the chain. But in the quinol series this is no longer true :



The push of the methyl now assists (b) and actually opposes (a). Hence the directive power of EtO (164) is higher than that found in the catechol series. And with larger groups it continues to increase (Pr^oO, 180; *n*-BuO, 186; *n*-C₁₆H₃₃O, 212).

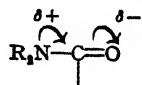
An electron-attracting group is p -nitrophenyl, and here the circumstances are reversed. In the catechol series NO₂·C₆H₄·CH₂O, 67, and in the quinol series, 38. The distributed pull on the electrons of the oxygen atoms in the former case results in a higher directive power than the pull in the latter case acting on the oxygen of the nitrobenzyloxy-group alone. One apparent exception was noted in the benzyloxy-group (113 in the catechol series, 107 in the quinol series), but the differences are small and the value in the catechol series is suspect. In the course of the Faraday Society discussion in 1923, it was stated that the polarity theories

explained everything and predicted nothing. The lecturer thereupon made a prediction as follows :

- (1) That the *para*-chlorobenzyloxy-group would have a greater orienting power than *meta*, and
- (2) that the *para*-nitrobenzyloxy-group would have a weaker orienting power than the *meta*.

In 1927 the first prediction was justified (*p*-, 82; *m*-, 69), but the *m*- and *p*-nitrobenzyloxy-groups had nearly the same directive powers (67), in the catechol series. The anticipated effect was, however, noted with the nitrobenzamido-groups in the acylated *p*-phenetidine series (EtO, 100; *p*-, 190; *m*-, 226).

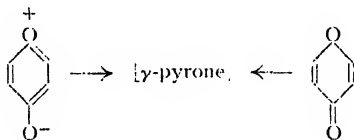
The Neutralised Systems.—If a strongly cationoid group is attached to a strongly anionoid group, e.g., N to CO, electron transfer occurs in the molecule under all conditions :



The result is in this case to diminish the basic character of N and the cationoid character of C of CO and to produce a definite dipole evinced by the physical character of the amides. In a similar way the characters of the carboxylic acids and their derivatives receive a very convincing explanation. As always the groups can be separated by one or more double bonds, and the extent of the neutralisation depends on the affinity of the nitrogen and oxygen, or what corresponds to them in other examples, for their respective charges.

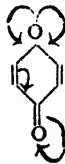
The Condition of Molecules in the Resting State.—Both Lapworth and the lecturer postulated a certain degree of polarisation in normal molecules of an unsymmetrical nature, but paid little attention to the matter because their chief concern was with reactions. The existence of electromeric displacements in the normal molecules of the conjugated complexes was, however, always mentioned in lectures in various centres on these topics and in University teaching from 1922. Indeed, the views expressed in regard to neutralised systems such as the amides, and the references to their physical and chemical properties, were meaningless without this assumption.

In the case of certain classes of compounds the idea was emphasised, and the pyrones, for example, were recognised as intermediate between the fully polarised hydroxypyrylium betaine and the usual neutral formula (Armit and Robinson, *J.*, 1925, 127, 1604) :



Arndt, Scholz, and Nachtwey (*Ber.*, 1924, 57, 1903) put forward a similar view of "Zwischenstufe" based on the properties of a series of thiopyrones. They did not interpret their hypothesis in terms of electronic displacements.

Another way of representing the matter is to say that the pyrones are normally



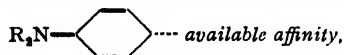
and it will be noticed that this is merely a neutralised system of ester type, $-O-CO-$, in which a double bond is interpolated in two places. There is, however, the additional circumstance that the pyrylium nucleus is aromatic, and that was considered to be an important factor in producing a closer approximation to the pyrylium betaine than would otherwise be the case.

Ingold and Ingold (*J.*, 1926, 1310) introduced the convenient term "mesomerism" for this electromeric effect in normal molecules, and an outstanding contribution on the experimental side was made by L. E. Sutton. Using the method of measurement of dipole moments he was able to recognise the mesomerism of many aromatic compounds containing hetero-

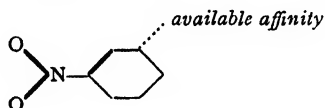
enoid and catio-enoid systems as well as those in which both are present and may be partly neutralised. The direction of the mesomeric displacement was not necessarily in the same sense as the dipole. Thus the dipole in chlorobenzene was in the direction $\text{Cl}-\text{C}_6\text{H}_5 \leftarrow$ as the

theory of the general effect demands. A small counteracting mesomeric effect $\text{Cl}-\text{C}_6\text{H}_5 \rightarrow$ was detected by comparison of the moment of chlorobenzene with that of *tert.*-butyl chloride (*Proc. Roy. Soc.*, 1931, **133**, 668). This work was a remarkable physical confirmation of the validity of the hypotheses which have briefly been expounded, for it was found that all *op*-directive groups examined increased the density of electrons in the aromatic nucleus and all *m*-directive groups decreased it. Methods for determining the occurrence and extent of mesomerism have been developed by Pauling and others, but they belong to the modern period. The device of writing down the possible structures and estimating the contribution which each makes to the actual condition of the molecule is a calculus and not a theory of structure, though it has often been misunderstood as such.

Conclusion.—Many important tributaries have been omitted from this account and the river has not been followed to the sea. Thus the work of Claus, Werner, and Flürscheim had a most important influence on the thoughts of chemists. Flürscheim's development of the theory of alternating and variable affinity was especially valuable. It gave the results now regarded as correct in many cases, as in the hetero-enoid systems :



but failed to meet our requirements in the catio-enoid systems :



The speculations of Vorländer and Fry likewise contained useful detailed suggestions but were eventually seen to be out of the direct line of progress. The lecturer has perforce had to omit all reference to the stereochemical aspects, such as the Mills–Nixon effect, to W. Baker's applications of chelation, to tautomerism, dissociating systems, and molecular rearrangement, as well as to many other topics of great interest. In particular he has not mentioned the neutral free radicals and atoms, which can be anionoid, *or* cationoid, *or* homopolar.

It seems peculiarly appropriate that a Faraday Lecture should deal with molecular electrical phenomena, although they are of a very simple kind, in relation to properties of the derivatives of benzene, a substance which Faraday discovered. We owe to him the first studies of dielectrics and as a twig from this tree we take the measurement of dipole moments. Above all he was a great electrochemist and was convinced that electricity and chemical affinity could be identified. His Laws of Electrolysis, considered from the point of view of atoms and ions, bear much the same relation to the atomic theory of electricity that the Law of Multiple Proportions bears to the atomic theory of the elements.

In the Faraday Lecture of 1881, Helmholtz said : " Now the most startling result of Faraday's Law is perhaps this. If we accept the hypothesis that the elementary substances are composed of atoms, we cannot avoid concluding that electricity also, positive as well as negative, is divided into definite elementary portions which behave like atoms of electricity ".

The logic is inescapable and yet we must admire the acumen and courage of the remark.

Without forgetting the work of Volta, Davy, and Berzelius, and of many other real pioneers in the middle and later periods, we are right to honour the memory of Michael Faraday, the most illustrious of the founders of a science of electrochemistry.

239. Theory of Chromatography. Part II.* Chromatograms of a Single Solute.

By E. GLUECKAUF.

Chromatograms of single solutes, in particular the case of sigmoid isotherms, are treated theoretically and measured experimentally. The form of the chromatograms resulting from the different isotherms and the movement of their characteristic points are shown and calculated (see Figs. 1—6). Adsorption and exchange isotherms can be calculated from chromatographic elution curves (see Figs. 7 and 9). Comparison of an isotherm, determined in this way, with directly determined equilibrium values shows a good agreement (see Fig. 5), and the chromatographic method gives a much larger number of points for less experimental work.

Symbols :

c , concentration in milliequivs. per c.c.

$q = f(c)$, amount of solute taken up by 1 g. of adsorbent (including pore space) in equilibrium with c (m.-equiv./g.).

$f^*(c) = q - ac$, the amount actually adsorbed on the adsorbent.

a , pore space per g. of adsorbent (c.c./g.).

v , volume of developing solution used (c.c.).

v^0, c^0, q^0 , volume and concentration of original solution, and amount adsorbed per g. in equilibrium with c^0 .

x , distance from the top of the column, measured in g. of adsorbent.

$m = v^0 c^0$, amount of solute used (m.-equiv.).

μ_c , amount of solute in the column behind a given point \bar{x} of concentration \bar{c} on the rear boundary.

μ_c' , amount of solute in front of a given point \bar{x} of concentration \bar{c} on the front boundary.

Indices in italics refer to characteristic points of the chromatogram, shown in the diagrams :

u to the undeveloped front (see Fig. 2, A, B).

w to the front of a fully developed chromatogram (see Figs. 2, C and 6, D).

s to the sharp undeveloped rear boundary (see Fig. 4, A).

r to the sharp rear boundary of a fully developed band (see Fig. 4, B).

o to the point of concentration 0 in a diffuse boundary (see Figs. 2, 4, 6).

d to the point of concentration c^0, q^0 in a diffuse boundary (see Figs. 2, 4, 6).

e, e', f , and e are used for points on a partially diffuse boundary (see Fig. 6).

(a) *Chromatographic Equations for Single Solute Isotherms.*—Chromatography is the name given to the process of separation by continuous fractional adsorption, because of its earlier applications to the separations of coloured substances, though this limitation no longer obtains. The normal procedure is to pour a solution of the solutes to be separated on to the top of a column filled with adsorbent and allow it to percolate into the column, a process which may be accelerated by applying suction at the bottom or, better, pressure at the top. After this original solution is taken up by the column, and has formed a band, further amounts of pure solvent are added at the top, dissolving the band of adsorbed solutes from the rear and slowly carrying it through the column, a process called "development." During the development stage the band usually spreads, whereby its local concentration decreases and, as the individual solutes move with different speed through the column, partial or complete separation takes place.

The regions in the front and rear of the adsorption band are called "boundaries," and these may be "sharp" or "diffuse" according to the type of adsorption isotherm obtaining for the particular case of adsorbent, adsorbate, and solvent. (The boundaries are always diffuse if the flow of solvent is too fast to permit local equilibrium to be reached; see Part IV.) In the case of multiple solutes the word "boundary" is applied to all parts where concentration gradients exist.

The movement of any type of boundary is governed by the principle of mass-conservation, which means that, if we consider the solute content of a very thin section of the chromatographic band, its increase (or decrease) is given by the difference of the inflowing and the outflowing solute.

The movement of the band can be considered in two ways.

We can mentally fix our eyes on a given particle of the solute. Then this point of fixed mass within the band of a single solute, the concentration of which may, e.g., be c^0 , moves with a given amount of solvent v according to (1) (see Wilson, *J. Amer. Chem. Soc.*, 1940, 62, 1583) :

$$[\Delta x / \Delta v]_m = c^0 / f'(c^0) \quad \dots \dots \dots (1)$$

Alternatively, we may follow the movement of a point of constant concentration in a diffuse boundary (see Fig. 2, C, curve A—B), which is described by equation (2) (see De Vault, *ibid.*, 1943, 65, 532; Weiss, *J.*, 1943, 297) :

$$[\Delta x / \Delta v]_c = dc / df(c) = 1 / f'(c) \quad \dots \dots \dots (2)$$

* For Part I, see *Proc. Roy. Soc.*, 1946, A, 186, 35.

Finally, we have the integrated equations for the amount of solute in the chromatogram between the concentrations \bar{c} and $c = 0$, which in the case of a diffuse rear boundary (see Fig. 2) is

$$\mu = \bar{x}f(\bar{c}) - v\bar{c} \quad (3)$$

(Glueckauf, *Nature*, 1945, 156, 748) and for a diffuse front boundary (see Fig. 4):

$$\mu' = (v + v^0)\bar{c} - \bar{x}f(\bar{c}) \quad (4)$$

FIG. 1.

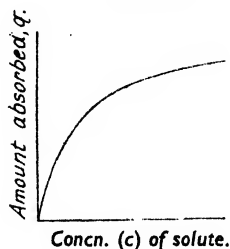


FIG. 2.

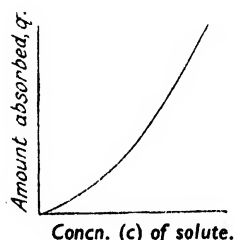
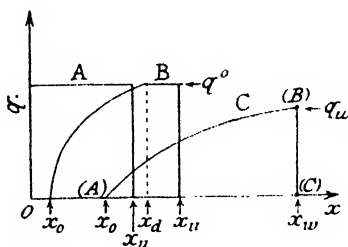


FIG. 3.

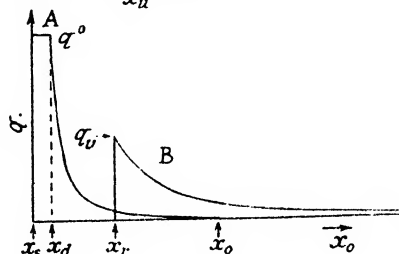


FIG. 4.

FIG. 1.—Normal isotherm concave against c -axis.

FIG. 2.—Development of a band of solute with isotherm as in Fig. 1.

Abscissa = distance from top of column.

Ordinate = amount absorbed per g. of column material.

(A) Original band. (B) Incomplete development. (C) Complete development. (A)–(B) Diffuse rear boundary, (B)–(C) sharp front boundary.

FIG. 3.—Isotherm convex against c -axis.

FIG. 4.—Development of a band of solute with isotherm as in Fig. 3.

(A) Original band. (B) Complete development.

Equation (3) actually comprises equation (1).

The combinations of these equations represent all the relevant conditions of the various parts of the chromatograms (some of which have already been given by Weiss, *loc. cit.*).

For an adsorption isotherm concave towards the c -axis (see Fig. 1) we get (for subscripts see Figs. 2, A, B, C):

$$x_0 = v/f'_{(0)} \quad (5a)$$

$$x_d = v/f'_{(c^0)} \quad (6a)$$

$$x_u = (v + v^0)c^0/f'_{(c^0)} \quad (7a)$$

$$x_w = m/(f'_{(c_w)} - c_w f'_{(c_w)}) \quad (8a)$$

where c_w is defined by

$$v = m f'_{(c_w)} / (f'_{(c_w)} - c_w f'_{(c_w)}) \quad (9a)$$

For an adsorption isotherm convex towards the c -axis (see Fig. 3) we get (for subscripts see Figs. 4, A, B):

$$x_0 = (v + v^0)/f'_{(0)} \quad (5b)$$

$$x_d = (v + v^0)/f'_{(c^0)} \quad (6b)$$

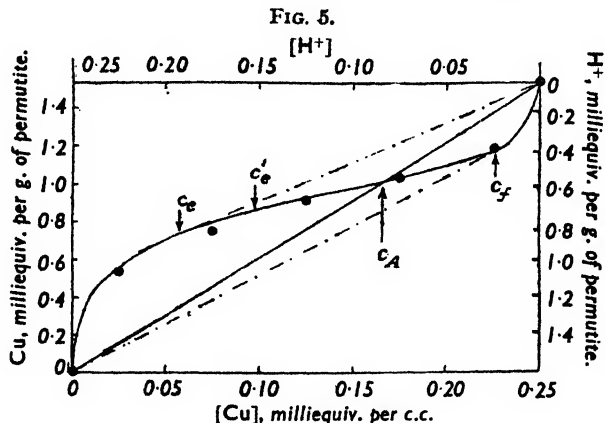
$$x_s = v c^0 / f'_{(c^0)} \quad (7b)$$

$$x_r = m / (c_r f'_{(c_r)} - f'_{(c_r)}) \quad (8b)$$

where c_r is defined by

$$v + v^0 = m f'_{(c_r)} / (c_r f'_{(c_r)} - f'_{(c_r)}) \quad (9b)$$

Slightly more complicated are the conditions in the case of sigmoid isotherms. These are particularly frequent in ion-exchange systems on zeolites, permutites, and exchange resins, in cases where both ions are taken up with similar affinity (see, *e.g.*, Rothmund and Kornfeld,



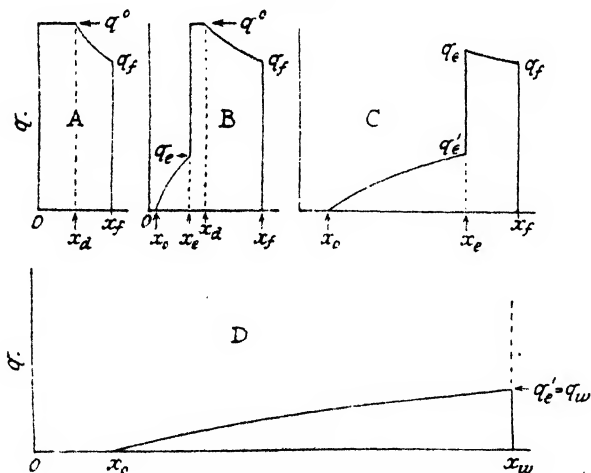
Example of sigmoid isotherm.

Exchange isotherm of H^+ and Cu^{++} on Zeo-carb H.I. for a total concentration in solution of 0.25N.

Abscissa: Cu^{++} concentration in solution (milli-equiv. per c.c.).
 Ordinate: Cu content of zeo-carb (milli-equiv. per g. of zeo-carb).
 Curve: isotherm obtained from chromatographic data.
 Points: isotherm points from direct equilibrium measurements.

Z. anorg. Chem., 1918, 103, 129, for the case of $Na-NH_4$ and $Ag-Tl$). Though two ions are involved in any isotherm, they can nevertheless be treated as simple systems, for, under the conditions of constant total concentration existing during the elution process, there is only

FIG. 6.



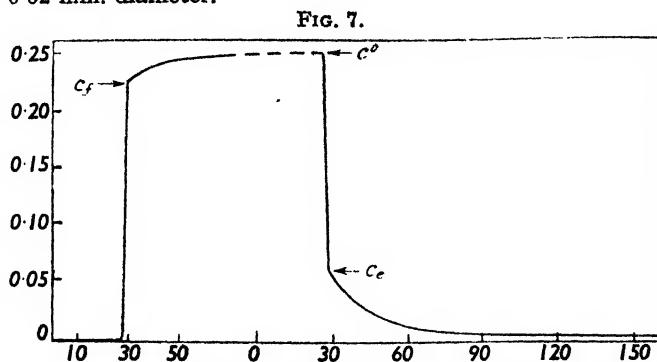
Development of a band of solute with sigmoid isotherm.

- (A) Original band. (C) First stage of development completed.
 (B) Development incomplete. (D) Complete development.

one freely variable concentration. Bands in every respect identical with those produced by adsorption phenomena are obtained by using a solution of the original cation of the permutite as developing agent.

In the case of sigmoid isotherms, chromatograms are obtained which, at first, have partly diffuse and partly sharp boundaries both in front and rear. In the later stages of the develop-

the recorder. (The residual cupric ion was eluted with $2N-H_2SO_4$, which removed it quickly, and then titrated.) To avoid non-equilibrium phenomena, the permutite material was ground to a grain size of 0.02 mm. diameter.

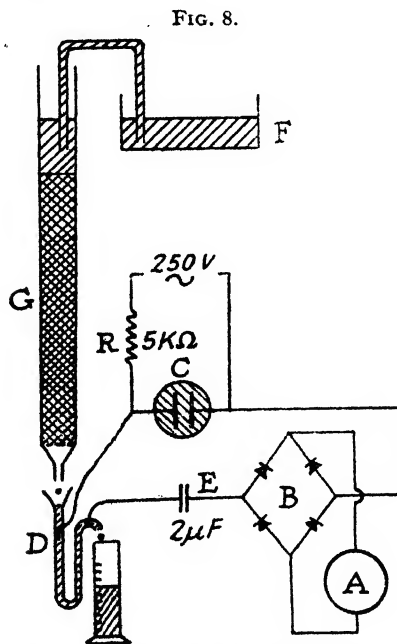


Measured elution curve of a solute with sigmoid isotherm.

Abscissa: volume of eluate (c.c.).

Ordinate: concentration of eluate, milliequiv./c.c.

(Compare with the band shown in Fig. 6B.)



Arrangement for the automatic registration of concentrations in the eluate.

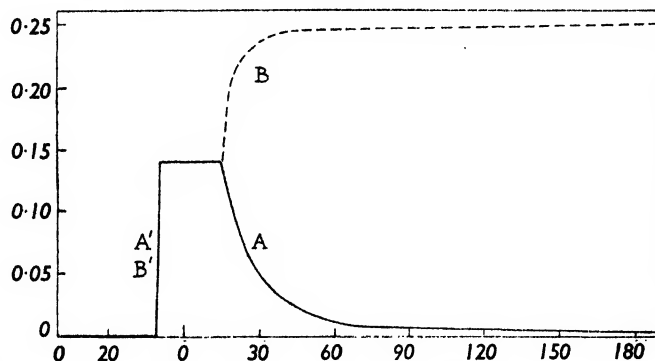
- (A) Recording μ -ammeter (0—100 μ A.).
- (B) Full-wave rectifier.
- (C) Neon voltage-stabiliser.
- (D) Capillary with Pt electrodes for resistance measurement of eluate.
- (E) Condenser 2μ F.
- (F) Constant level for constant dropping speed.
- (G) Column filled with 5 g. of Zeo-carb.
- (R) 5000 Ω resistance.

The eluate consists at first of $0.25N-H_2SO_4$. The front of the copper arrives at a threshold volume $v_t = 29$ c.c. Its concentration rises sharply to a value of $c_f = 0.225$, as one would expect from the theory (eqn. 12) which fixes this concentration as the point where the tangent from the origin ($c = 0$), touches the isotherm (see Fig. 5). Thence the concentration rises asymptotically to the original value $c^0 = 0.25$ milliequiv./c.c.

After passing a sufficiently large amount of copper solution through the column to convert the zeo-karb completely into Cu-zeo-karb, this "undeveloped band" was now "developed" with 0.25N-H₂SO₄, whereby the rear boundary of the copper band was obtained. Here, too, the concentration fell at first sharply to a value of $c_e = 0.060$ milli-equiv./c.c. [which again is in agreement with the theory (eqn. 14), representing the point in Fig. 5 where the tangent from the point $c^0 = 0.25$ milliequiv./c.c. touches the exchange isotherm]. With continued elution, the copper concentration exhibits the normal behaviour and falls asymptotically to zero (see Fig. 7).

Thus the greater part of the isotherm, between $c_e = 0.060$ and $c_f = 0.225$, cannot be calculated from the chromatographic data of this experiment, as these concentrations do not appear in the chromatogram. Boundaries covering the whole concentration range can, however, be obtained by saturating the column with solute of the concentration (c_i) existing at the point of inflexion (or near by), and then (i) eluting with pure solvent (acid) and (ii) saturating the column with the concentration c^0 . From the first experiment (elution of a copper band) results a diffuse rear boundary which permits the calculation of the adsorption data between c_i and 0; in the second case (elution of an acid band) is obtained a diffuse boundary between c_i and c^0 .

FIG. 9.



Measured "elution curves" of a solute with sigmoid isotherm, suitable for determination of the isotherm by means of eqn. (3) or (4).

TABLE I.

(From curve A, Fig. 9.)

v (obs.).	c (obs.).	$\Delta\mu$.	μ .	$(v - \alpha x)c$.	$x f^*(c)$.	$f^*(c)$.
14.5 = V_i	0.140	0.56	3.62	1.19	4.81	0.962
19.1	0.103	0.49	3.06	1.35	4.41	0.882
24.9	0.066	0.31	2.57	1.25	3.82	0.764
30.6	0.044	0.22	2.26	1.08	3.34	0.668
36.4	0.033	0.17	2.04	1.00	3.04	0.608
42.1	0.028	0.17	1.87	1.01	2.88	0.576
63.1	0.010	0.40	1.47	0.57	2.04	0.408
166	0.005		0.73	0.80	1.53	0.306

TABLE II.

(From curve B, Fig. 9.)

$v + v^0$.	c .	$\Delta\mu$.	μ .	$(v + v^0 - \alpha x)c$.	$x f^*(c)$.	$f^*(c)$.
15.3 = V	0.140	0.18	2.14	1.30	4.81	0.962
16.5	0.166	0.37	2.32	1.74	5.08	1.016
18.5	0.200	0.41	2.68	2.50	5.47	1.094
2.04	0.213	1.17	3.07	3.07	5.65	1.130
25.6	0.227	2.04	4.19	4.45	5.91	1.182
34.0	0.237		6.15	6.71	6.21	1.242
∞	0.250		—	—	7.50	1.500

Italicised values are measured directly. Other values of cols. 1, 2, 3 are taken from the registered elution curves. Col. 6 in Table I is the sum of cols. 4 + 5. Col. 6 in Table II is (5.65 + col. 5 - col. 4). The figure 5.65 represents $(f^*(c_i) + \alpha c^0)x$, i.e., the amount of solute in the column at the time of the change-over. $\Delta\mu$ is the eluate between two evaluated points, i.e., the product of Δv and the average concentration. The amount μ left in the column is obtained by adding all the $\Delta\mu$'s to the amount finally left in the column and measured directly.

In either case no discontinuous "rear" boundaries are obtained, because from this point (c_i) no tangent can be drawn to any other part of the isotherm.

The elution curves shown in Fig. 9 A, B are obtained in the following way: Through a column of acid Zeo-karb (5 g.) was passed a solution of $0.14N\text{-CuSO}_4 + 0.11N\text{-H}_2\text{SO}_4$ which approximately corresponds to the mixture at the point of inflexion of the isotherm. The copper arrived in the eluate with a sharp front boundary ($v_t = 40$ c.c.). Then the solution was changed, $0.25N\text{-H}_2\text{SO}_4$ (see curve A) being used for the elution of the copper, and (see curve B) in a second experiment $0.25N\text{-CuSO}_4$ for the elution of the hydrogen ions. In either case a diffuse rear boundary was obtained beginning at about 14.5 and 15.3 c.c. respectively after the change-over.

From these two curves the complete exchange isotherm can be calculated. Curve A can be evaluated according to eqn. (3):

$$f^*(\bar{c}) = [\mu_c + (v - \alpha x)\bar{c}]/x \text{ (see Table I).}$$

Curve B can be evaluated in two ways: It can be considered as the rear boundary of a hydrogen-ion band, and then eqn. (3) applies, with c referring to the hydrogen-ion concentrations. Alternatively, it can be considered as the partial front of a pure copper-ion band moving against a mixed solution, in which case eqn. (4) applies [though with some modification on account of the chromatographic tube containing originally some Cu (c_0)]. Integration for these conditions leads to:

$$f^*(\bar{c}) = f^*(c_0) + [(v + v^0 - \alpha x)\bar{c} - \mu_c]/x$$

where $f^*(c_0)$ is obtained from Table I, or from the threshold volume $v_t = 40$ (frontal line A'B' of Fig. 9) by means of

$$f^*(c_0) = v_t c_0/x - \alpha c_0 \text{ (see eqn. 1a).}$$

From the experimental data ($v_t = 40.0$ c.c., $c_0 = 0.140$, $x = 5$ g., $\alpha = 1.20$ c.c./g.) follows a value for $f^*(c_0) = 0.953$ milli-equiv./g., in good agreement with 0.962 found from Table I. The agreement of the equilibrium values of the exchange isotherm calculated in Tables I and II is shown in Fig. 5. Here the continuous curve represents the isotherm obtained by the chromatographic method, and circles mark points determined by direct equilibrium measurements. The obvious advantage of the chromatographic method of measuring isotherms, especially if the concentration of eluate can be measured continuously, is that a single experiment gives an almost unlimited number of equilibrium points of the isotherm.

(c) *Gas Adsorption Columns* (added in proof, August, 1947).—The considerations about the distribution of solutes in an adsorption column apply equally to the case of gases adsorbed from an air stream in adsorption columns. In the recently published experimental observations of Barrow, Danby, Davoud, Hinshelwood, and Staveley (this vol., p. 401), the different cases of Figs. 1 and 2, A and of Figs. 3 and 4, A are found when air containing carbon tetrachloride and water vapour respectively is passed through a charcoal column. The removal of the adsorbates from the column by passing clean air through (see their Figs. 7, 8, and 11, 12) corresponds to a development with pure solvent and is represented by Figs. 2B, C and 4B of this paper and by the corresponding equations. The above-mentioned experiments with gases also show clearly the effect of non-equilibrium phenomena, which are more fully discussed in Part IV.

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[Received, November 20th, 1946.]

240. Theory of Chromatography. Part III. Experimental Separation of Two Solute and Comparison with Theory.

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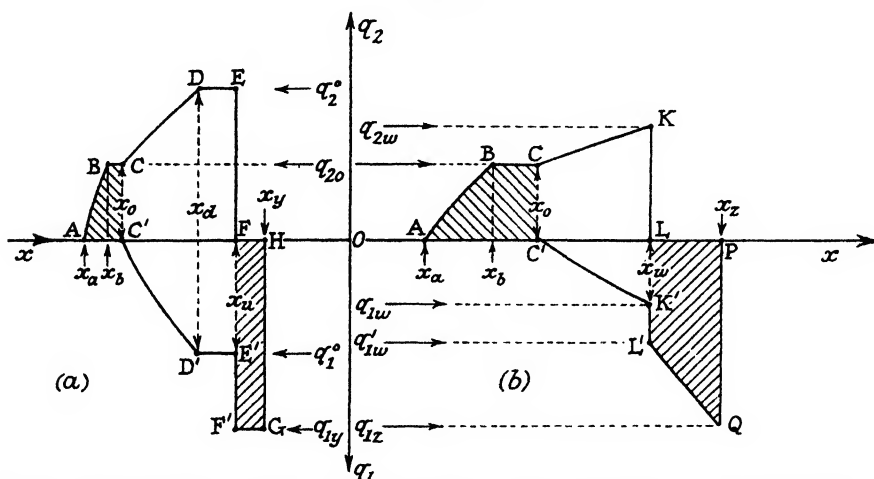
The results obtained in Part I (*Proc. Roy. Soc.*, 1946, A, 186, 35) for chromatograms of two solutes are summarised in Tables I—V, giving the features and movements of the important parts of binary chromatograms (see Fig. 1) at various stages of the development. The results are given both for the general case and for the special case of the Langmuir isotherm.

The agreement of these calculations with quantitative elution experiments is shown for a chromatographic separation of Cu^{++} and Mn^{++} on Zeo-karb H.I. (see Fig. 2, 3, and 4), the exchange of which follows approximately an isotherm of the Langmuir type.

(a) *Summary of Part I.*—A normal binary chromatogram has, according to whether it is fully developed or not, a distribution of solutes as shown in Fig. 1b and 1a, respectively. (Some

modifications may occur if the isotherm has an infinite slope at zero concentrations, as, e.g., in the case of the Freundlich isotherms; see Part V.) The movement of any given point of such a chromatogram can be given in general mathematical terms, but only in the case of the Langmuir isotherm (see eqn. 1) can the essential differential equation (2), defining the relationship of coexistent concentrations c_1 and c_2 in the mixed band, be solved. Once this function is known for a given case of initial concentrations c_1^0 and c_2^0 , the adsorption isotherm $q_1 = f_1(c_1, c_2)$ can be replaced in the mixed band by the pseudo-isotherm $q_1 = F_1(c_1)$ (eqn. 3), so that the problem is thereby reduced to the case of a single solute isotherm. In this way the difficulty mentioned by de Vault (*J. Amer. Chem. Soc.*, 1943, 65, 532) of obtaining the full differential $df_{1(c_1, c_2)}/dc_1$ is being solved. The essential data for the development of a binary chromatogram are given in Tables I—V, with full reference to the corresponding parts in Fig. 1a, b. In these tables, the pore space of the adsorbent has not been considered. Correction for this can be made by

FIG. 1.



Diagrammatic representation of binary chromatogram (a, partly developed; b, fully developed), showing the amounts q_1 and q_2 adsorbed per g. of adsorbent at various distances x from the top of the column. The subscripts and figures are referred to in Tables III—VII giving quantitative information on the movements of points and boundaries.

The pure front band of solute 1 and the pure rear band of solute 2 are hatched.

substituting $(v - \alpha x)$ for v , or by replacing $f_{(c)}$ by $f_{(c)} + \alpha c$, whichever is more convenient. The equations may be used for the calculation of both chromatograms and elution curves according to whether they are applied to a constant value of v (giving a relation between the "length" x and c) or to a constant value of x , the total adsorbent in the column (giving a relation between the volume of eluate v and its concentration c).

(b) *Conclusions of Practical Interest derived from the Equations of Part I for Separation of Two Solutes.*—(1) For the Langmuir type of isotherm, separation is facilitated by working at high adsorption densities, but no advantage is derived from using high solute concentrations when the adsorbent is already fairly saturated.

(2) If this is done, the amount of adsorbent and also the amount of developing solution required for complete separation are proportional to $(m_1 + m_2)$, i.e., to the total quantity of the solutes. A rough practical rule for the minimum amount X_0 of adsorbent required for complete separation would be $X_0 = L^0/(\Delta x_1/\Delta x_2 - 1)^2$ where L^0 is the amount of adsorbent taken up by the original undeveloped band, and Δx_1 and Δx_2 are the displacements of the rear of the pure single-solute bands produced by equal amounts of developing solvent; Δx can easily be determined if the pure solutes are available. More than the amount X_0 is required for a good spatial separation of the bands.

(3) If solutes are so difficult to separate that no complete separation, but only enrichment can be achieved, it is always an advantage to develop with a solution containing a third and more strongly adsorbed solute of at least equal concentration. Here the amount of adsorbent required to separate the solutes is approximately only $X_0 = L^0/(\Delta x_1/\Delta x_2 - 1)$ but, as the two bands do not separate, a mixed band always remains on account of non-equilibrium effects

(see Part IV). The displacements Δx_1 and Δx_2 have to be determined in the absence of the third solute. It is obvious that development with a third solute gives the advantage of requiring shorter columns only if $(\Delta x_1/\Delta x_2 - 1) \ll 1$. Other advantages of using a third solute, like the greater mobility in the case of very strongly adsorbed solutes, are independent of this consideration.

EXPERIMENTAL

The experiments were carried out with columns containing 60 g. of acid Zeo-karb H.I. The attainment of equilibrium (see subsequent paper) is of particular importance in the case of chromatography with ion exchangers, for the diffusion in these is somewhat slower than, e.g., in alumina. However, by using a grain size of 0.01 mm. diameter and a flow velocity of 0.001 cm./sec. (corresponding to one drop in two minutes), elution curves were obtained which were even better than those obtainable with the apparently faster alumina of equal grain size. This seems to be due to a different effect altogether. Acid Zeo-karb when taking up larger ions like copper or manganese, undergoes a noticeable

TABLE I.

Fundamental equations.

	General isotherm.	Langmuir isotherm.
Adsorption isotherm	$q_1 = f_1(c_1, c_2)$ $q_2 = f_2(c_1, c_2)$	$q_1 = a_1 c_1 / (1 + b_1 c_1 + b_2 c_2)$ $q_2 = a_2 c_2 / (1 + b_1 c_1 + b_2 c_2)$. . . (1)
Condition for coexistent concentrations in the mixed band	$df_1(c_1, c_2)/dc_1 = df_2(c_1, c_2)/dc_2$ can be integrated graphically for a given case of c_1^0 and c_2^0 (see Part V)	$a_2 b_1 c_1 = a_1 b_2 c_2 \lambda - (a_2 - a_1) \lambda / (1 + \lambda)$, where λ can be obtained from the same equation with $c_1 = c_1^0$ and $c_2 = c_2^0$. In the following, λ is considered a known constant (2)
Pseudo-adsorption isotherms in mixed band	$q_1 = F_1(c_1)$ $q_2 = F_2(c_2)$ $\left\{ \begin{array}{l} \text{obtainable from} \\ \text{relationship} \\ \text{between coex-} \\ \text{istent values} \\ \text{of } c_1 \text{ and } c_2 \end{array} \right.$	$q_1 = A_1 c_1 / (1 + B_1 c_1)$ $q_2 = A_2 c_2 / (1 + B_2 c_2)$ where $A_1 = a_1(1 + \lambda) / (1 + \lambda + \delta)$ $B_1 = b_1(1 + \lambda) / \lambda$ $A_2 = a_2(1 + \delta)(1 + \lambda) / (1 + \lambda + \delta)$ $B_2 = b_2(1 + \lambda)$ $\delta = (a_2 - a_1) / a_1$ (3)
Movement of a given mass-point of solute 1 (and <i>vice versa</i> for solute 2) in the mixed band	$\left[\frac{\Delta x}{\Delta v} \right]_{m_1} = c_1 / f_1(c_1, c_2) = c_1 / F_1(c_1)$	$= (1 + b_1 c_1 + b_2 c_2) / a_1 = (1 + B_1 c_1) / A_1$. . . (4)
Movement of point of given concentrations c_1, c_2 in a diffuse boundary	$\left[\frac{\Delta x}{\Delta v} \right]_{c_1, c_2} = 1 / F'_1(c_1) = 1 / F'_2(c_2)$	$= (1 + B_1 c_1)^2 / A_1 = (1 + B_2 c_2)^2 / A_2$ (5)
Amount of solute in the chromatogram between the points of concentrate c and $c = 0$ (c within the mixed band)	$m_{1(a-x)} = x f_1(c_1, c_2) - v c_1$ $m_{2(a-x)} = x f_2(c_1, c_2) - v c_2$	Same (6)

TABLE II.

Important concentrations in the chromatogram (see Fig. 1a, b).

	General isotherm.	Langmuir isotherm.
c_{20}	Obtainable from graphical integration	$c_{20} = \delta / B_2$ (7)
c_{1y}	Obtainable from $\frac{c_{1y} - c_1^0}{c_2^0} = \frac{f_1(c_{1y}) - f_1(c_1^0, c_2^0)}{f_2(c_1^0, c_2^0)}$	$c_{1y} = c_1^0(1 + \lambda) / \lambda$ $\approx c_1^0 + c_2^0 - c_{20}$ (8)
c_{2w}	Obtainable from $v = m_2 \frac{F'_2(c_{2w})}{F'_2(c_{1w}) - c_{2w} F'_2(c_{1w})}$	$c_{2w} = \sqrt{(m_2 / B_2 v)}$ (9)
c_{1w}	Obtainable from c_{2w} by means of the graphically obtained $c_1 - c_2$ relation	$c_{1w} = \lambda(a_1 b_2 / a_2 b_1) c_{2w} - \lambda(a_2 - a_1) / a_2 b_1 (1 + \lambda)$ $\approx \lambda(c_{2w} - c_{20})$ (10)
c'_{1w}	Obtainable from c_{1w} by $\frac{c'_{1w} - c_{1w}}{c_{2w}} = \frac{f_1(c'_{1w}) - F_1(c_{1w})}{F_2(c_{2w})}$	$c'_{1w} = c_{1w}(1 + \lambda) / \lambda$ $\approx c_{1w} + c_{2w} - c_{20}$ (11)
c_{1s}	Obtainable only by graphical evaluation according to	$\int_{x_0}^x q_1 dx = m_1$ (12)

The corresponding values of q are obtainable from c by means of eqn. (1).

TABLE III.

Equations for the different chromatographic boundaries (see Fig. 1a, b).

Type of boundary.	Ref. for Fig. 1 a, b.	General isotherm.	Langmuir isotherm.
Rear boundary of pure solute 2	$A - B$	$v/x = [\delta f_{1c_1} / \delta c_{1c_1}]_{c_1=0}$	$v/x = a_2/(1 + b_2 c_2)^2$ (13)
Rear boundary of solute 2 in mixed band (developed)	$C - D$ and $C' - K'$	$v/x = F'_{2c_2}$	$v/x = A_2/(1 + B_2 c_2)^2$ (14)
Rear boundary of solute 1 in mixed band (developed)	$C - K'$ and $C' - K'$	$v/x = F'_{1c_1}$	$v/x = A_1/(1 + B_1 c_1)^2$ (15)
Rear boundary of pure solute 1 in fully developed frontal band	$L' - Q$	$x = \frac{v}{f'_{1c_1}} + \frac{f'_{1c_1}(F'_{2c_2} - F'_{2c_{2w}})}{f'_{1c_1}(F'_{2c_{2w}} - c_{2w}F'_{2c_{2w}}) - c_{2w}F'_{2c_{2w}}}$ Where c_{2w} is a function of c_1 such that if $c_1 = c_{1w}$ then c_{2w} is the corresponding c_{2w}	$x = v(1 + b_{1c_1})^2/a_1 + \delta m_2 b_2(1 + b_{1c_1})^2/a_1(\delta + b_2 c_1)^2$ (16)
Front of mixed band (undeveloped)	$E - F'$ $E' - F'$	$x_w = (v + v^0)c_2^0/f_{2c_1} c_2^0$	$x_w = (v + v^0)(1 + b_{1c_1}^0 + b_{2c_2}^0)/a_2$ (17)
Front of mixed band (developed)	$K - L$ $K' - L'$	$x_w = m_2/(F'_{2c_{2w}} - c_{2w}F'_{2c_{2w}})$ (see c_{2w})	$x_w = [\sqrt{(v/A_2)} + \sqrt{(m_2 B_2/A_2)}]^2$ (18)
Front of pure solute 1 (undeveloped)	$G - H$	$x_y = (v + v^0)c_{1y}/f_{1c_1y}$ (see c_{1y})	$x_y = (v + v^0)(1 + b_{1c_{1y}})/a_1$ (see c_{1y}) (19)
Front of pure solute 1 (developed)	$Q - P$	Graphical solution only (see c_{1y})	— (20)

TABLE IV.

Amount of solute in different parts of the chromatogram.

Part of chromatogram.	Ref. to Fig. 1a, b.	General isotherm.	Langmuir isotherm.
Pure rear band of solute 2 (developed or undeveloped)	Area $ABCC'$	$v \frac{(F'_{2c_{2w}} - c_{2w} \cdot F'_{2c_{2w}})}{F'_{2c_{2w}}}$	$v \delta^2/B_2$ (21)
Pure front band of solute 1 (undeveloped)	Area $FE'F'GH$	$(v + v^0)c_1^0(1 - c_2^0 \cdot f_{1c_1} c_1^0 / c_1^0 \cdot f_{2c_2} c_2^0)$	$(v + v^0)c_1^0(a_2 - a_1)/a_2$ (22)
Solute 1 in mixed band (developed)	Area $C'K'L$	$v(F'_{1c_{1w}} - c_{1w}F'_{1c_{1w}})/F'_{1c_{1w}}$ (see c_{1w})	$B_1 v c_{1w}^2$ (see c_{1w}) (23)

The other parts are obtainable by difference from m_1 or m_2 .

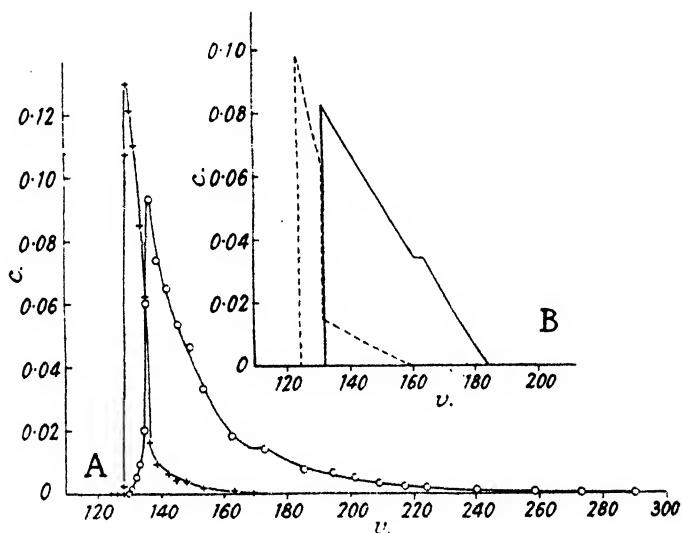
TABLE V.

Conditions for complete separation.

	General isotherm.	Langmuir isotherm.
Minimum amount of adsorbent required	$X_0 = m_2/(F_2(c_{20}) - c_{20}F'_2(c_{20}))$	$X_0 = m_2B_2/A_1\delta^2$ (24)
Minimum volume of developing solvent required	$V = m_2/(F_2(c_{20})/F'_2(c_{20}) - c_{20})$	$V = m_2B_2/\delta^2$ (25)

swelling, which has a stabilising effect on the front boundary of the ion band. For instance, if one side of the boundary should get in advance of the rest, the flow resistance on this side increases on account of the swelling, so that the other parts of the boundary can catch up. The effect is so marked that an ion band can be passed through a 1 m. column of 1" diameter, without showing a noticeable tilt in the circular front boundary.

FIG. 2.



Eluted chromatogram (fully developed) for partial separation of (1) Mn^{++} and (2) Cu^{++} on 60 g. of Zeo-karb H.I. Development with 1N- H_2SO_4 . Experimental conditions: $m_1 = 0.6$ milliequiv., $m_2 = 2.0$ milliequiv., $c_1^0 = 0.1N$, $c_2^0 = 0.4N$. Isotherm constants: $a_1 = 2.12$, $b_1 = 2.3$, $a_2 = 2.35$, $b_2 = 2.56$. $\alpha = 0.7$ c.c./g. Grain size of Zeo-karb 0.01 mm. Flow velocity ~ 100 c.c./24 hours. Note the exceedingly sharp front boundary due to reduction of non-equilibrium phenomena.

(B) Elution curve calculated with the equations of Tables I—III for a Langmuir isotherm with the above constants.

The columns used had a diameter of 1 cm. and were filled with suspended acid Zeo-karb H.I., the usual method of tapping and stuffing being employed. Equally good results were obtained if the tubes were filled with large quantities of material at a time, these being allowed to settle while the whole tube was subjected to constant vigorous vibrations by means of a bell movement clamped to the tube. This method saves much labour with large tubes and produces a very uniform sedimentation of the particles.

The elution curves were obtained by collecting, with an automatic device, fractions of the eluted solution, and analysing these by titration. Within the limits of the analytical error, the recovery of the solutes from 60 g. of Zeo-karb appeared to be 100%, but varying losses were obtained when working with alumina (see also Jacobs and Tompkins, *Trans. Faraday Soc.*, 1945, **41**, 403, Fig. 4).

Results.—Considerable difficulty was experienced in finding a binary system which follows a Langmuir isotherm (see eqn. 1). The nearest approach was found in the exchange isotherms of cupric, manganese, and hydrogen ions on exchange resins (Zeo-carb H.I. and H.I.P) for 1N. and higher total concentrations, and then only when more than 50% of hydrogen ions were present. For a lower hydrogen-ion ratio, the isotherm attains a sigmoid form, and for lower total concentration it changes increasingly towards the Freundlich type (see Part II, Fig. 5). However, within the region of

$$[Cu] + [Mn] < [H]$$

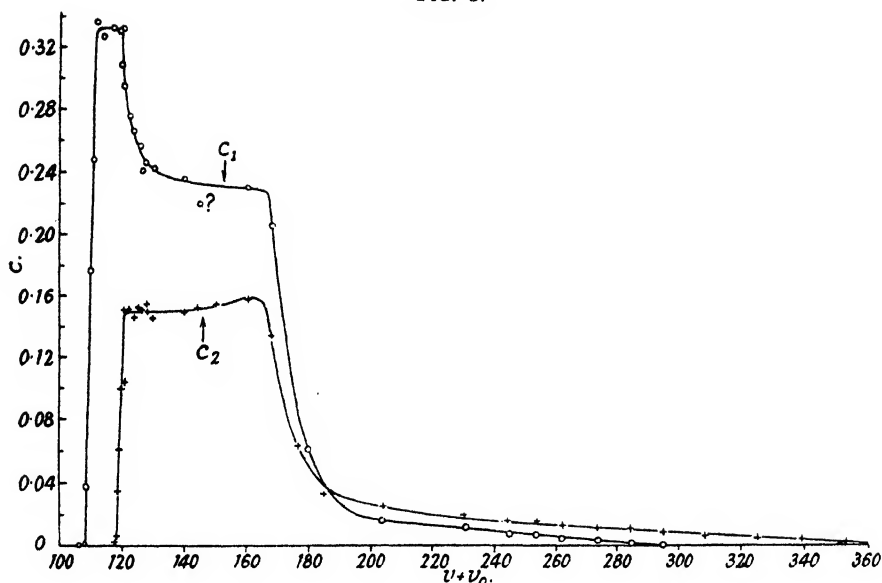
and

$$[Cu] + [Mn] + [H] = 1 \text{ milliequiv./c.c.} \quad . \quad . \quad . \quad (26)$$

the exchange isotherm can be well represented over the greater part of its course by equations of the type

$$q_{Mn} = q_1 = K_1[Mn]/([H] + K_2[Mn] + K_3[Cu]) \quad . \quad . \quad . \quad (27)$$

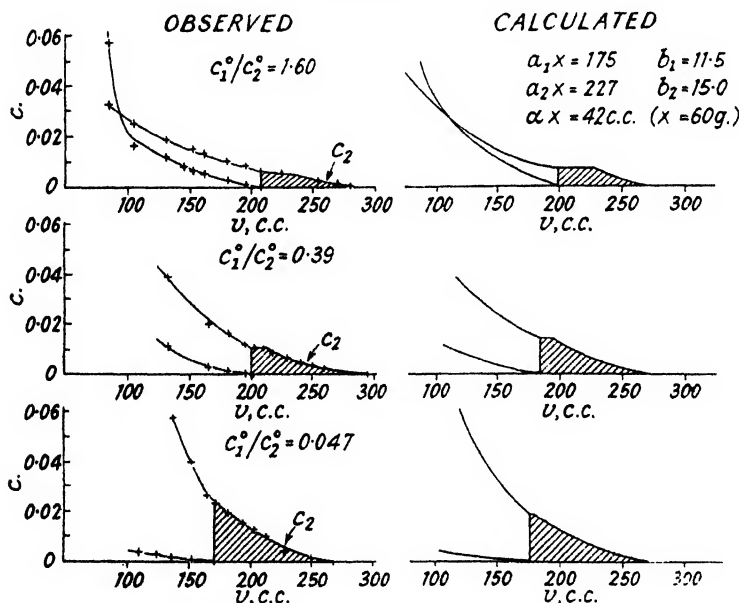
FIG. 3.



Elution curve for two solutes (development incomplete.)

Eluted chromatogram ("development" incomplete) of (1) Mn^{++} and (2) Cu^{++} on 60 g. acid Zeo-karb H.I. Development with 1N- H_2SO_4 . $c_1^0 = 0.23\text{N}$, $c_2^0 = 0.16\text{N}$.

FIG. 4.



Observed and calculated rear boundary effects for different ratios of the initial concentrations c_1^0/c_2^0 . Note that the form of and amount separated in the pure rear band depends on c_1^0/c_2^0 . Calculation acc. to Tables I—IV.

and vice versa for q_{0u} . Eliminating $[\text{H}]$ by means of the condition of constant total concentration (eqn. 26) we obtain Cu-Mn isotherms

$$q_{\text{Mn}} = K_1[\text{Mn}]/\{1 + (K_3 - 1)[\text{Mn}] + (K_4 - 1)[\text{Cu}]\} \quad . \quad . \quad . \quad 28)$$

and similarly for q_{Ca} . These equations are formally identical with the Langmuir isotherm (eqn. 1).

At the very lowest metal concentrations [$(c_1 + c_2) < 0.03N$], rather more metal ions are taken up than correspond to the rest of the isotherm, which means that at the lowest concentrations all the constants a and b become larger.

Apart from reasons of their simple determination, copper and manganese had been chosen because they represent solutes which are, on this adsorbent, very difficult to separate. Their exchange affinities differ less than those of nickel and cobalt on alumina and they thus afford a particularly stringent test for both theory and practice.

Fig. 2A shows the measured elution curve of a manganese-copper separation in a column 1 m. long containing 60 g. of acid Zeo-karb H.I. In spite of the considerable length of column and the consequent increase of all disturbing factors, the theoretically vertical front boundaries were found to be exceedingly sharp—not only did the self-sharpening front boundary of pure manganese rise up within 1 c.c. of eluate, but even the practically non-self-sharpening front boundary of the copper against the frontal band of manganese is almost completely contained within 2 c.c. of eluate. It can therefore be assumed that equilibrium is almost complete at every point of the column. (For a detailed discussion on non-equilibrium phenomena at boundaries, see Part IV.)

Fig. 2B gives the elution curve calculated on the basis of the given constants (see legends of Fig. 2) by means of the equations deduced in Part I (*loc. cit.*) which are summarised at the beginning of this paper. In these calculations the pore space $\alpha = 0.7$ c.c./g. of adsorbent, which had been determined by direct measurement, has been taken into consideration.

The agreement between experiment and calculation is quite good except at the tail end of the chromatogram where the concentrations are very low and where, as mentioned before, the constants of the isotherm become larger. As a result, the tail is considerably longer than would be the case for a "pure" Langmuir isotherm and the concentration (c_{20}) at the front of the pure rear band of solute 2 is consequently reduced. Agreement is particularly good for the front part of the chromatogram, in particular for the threshold volume, and the sharp rise in the concentration of solute 1 at the inter-front (at $v = 36$ c.c.), which is to be expected for solutes of very similar adsorption affinity, is clearly shown.

The not inconsiderable disagreement in the details of the rear boundaries is of particular interest, because it shows the enormous sensitivity of the form of the rear boundary against minor variations in the form and shape of the isotherm.

If the isotherm is calculated from the rear boundaries of both the experimental and the calculated elution curve on Fig. 2, the two isotherms are practically indistinguishable between the concentrations of 0.02 to 0.09 milliequiv./c.c., as is seen from the following data :

[Cu].	q_{Ca} (milli-equiv./g. of Zeo-karb).	
	Calc. from exp. chromatogram.	Calc. for Langmuir isotherm.
0.093	0.176	0.175
0.065	0.130	0.1315
0.038	0.083	0.0835
0.019	0.046	0.044
0.006	0.017	0.014
0.002	0.007	0.005

The difference at the very lowest concentrations, which are practically inaccessible to ordinary equilibrium measurements, can thus with the greatest ease be recognised and calculated from the rear boundary of a chromatogram.

It is apparent therefore that, with the exception of threshold values, there is little hope of being able to calculate the shape of chromatograms if only the approximate forms of the isotherms are known. The value of the theory lies rather in the opposite direction in that it provides a convenient tool for the calculation of the isotherms, in particular of multiple isotherms from chromatographic data.

An example of a chromatogram where "development" has not been completed is shown in Fig. 3. Here the two front boundaries rise up steeply within about 3 c.c. of eluate. There follows the flat non-developed section, after which a rapid fall in the concentrations of both solutes takes place which, owing to small deviations in the isotherm, is again sharper than one would expect for the Langmuir type.

Fig. 4 shows the details of a few measured rear boundaries. Though relatively less important for the technical separation, these rear parts form a good test of the theory. Both c_{20} and the amount μ_2 separated at the rear are, according to the theory, dependent on the ratio c_1^0/c_2^0 of the initial concentrations, which in these three experiments have been varied over a wide ratio. The agreement between the calculated and the observed elution curves is as good as can be expected. Not only c_{20} and μ_2 , but also the form of the rear band of pure solute 2 and the position of the point where solute 1 becomes zero, clearly show the trend demanded by theory.

241. Theory of Chromatography. Part IV. The Influence of Incomplete Equilibrium on the Front Boundary of Chromatograms and on the Effectiveness of Separation.

By E. GLUECKAUF and J. I. COATES.

It is shown that in the chromatographic column, under the usual working conditions, complete local equilibrium is not obtained. A theory is developed for the effect of incomplete equilibrium on chromatographic boundaries, and the form of observed boundaries agrees with those calculated. On decrease of grain size and flow velocity, equilibrium becomes more complete, and then some chromatographic separations can be effected with ease which are impossible by the usual methods; e.g., the separation of nickel and cobalt ions on alumina.

(a) *Chromatographic Boundaries.*—The influence of incomplete local equilibrium is very similar to a diffusion effect and so shows itself most markedly at the boundaries of the chromatograms where high concentration gradients exist. Normal binary chromatograms when fully developed have, in the absence of disturbing effects, the form shown in Fig. 1 of the preceding paper. We may distinguish here two types of boundaries: (i) sloping rear boundaries such as AB , CD , and $C'D'$, and $L'Q$, and (ii) sharp front boundaries such as the threshold boundary HG or PQ and the inter-boundary EF , $E'F'$ or LK , $L'K'$ which is the front of solute 2. As has been shown by De Vault (*J. Amer. Chem. Soc.*, 1943, 65, 532) the two front boundaries have normally (i.e., for isotherms concave against the c -axis) self-sharpening properties. This means that, even if by some artificial means HG were made sloping, it would again become vertical during the process of development—at least theoretically. This self-sharpening tendency increases with the curvature of the isotherm and it is nil for linear isotherms (see De Vault, eqn. 7).

In the case of the threshold boundary HG , the self-sharpening effect is usually very considerable, as linear single-solute isotherms are rare. In the case of the inter-boundaries EF the corresponding function depends essentially on the "exchange" isotherm between the two solutes. If the two solutes are very different and easily separable, this boundary, too, usually shows considerable self-sharpening, but if the two solutes are very similar, the exchange isotherm is practically linear and then this effect is negligible. The inter-boundary is then referred to as a non-sharpening front boundary.

(b) *Attainment of Complete Equilibrium.*—In order to study the effect of non-equilibrium and diffusion phenomena, chromatographic elution curves were measured, using adsorbents of different grain size. The adsorbents were ground to a diameter as low as 0.01 mm. (as compared with the commercial grain sizes of about 0.08 mm.), and a uniform grain size was obtained by elutriation in air streams of varying velocity.

The flow rate of the solvent in the chromatographic column was varied from 0.001 cm./sec., which means 1 drop in 2 mins. for a tube of 1 cm. diameter, to the usual flow rates of 10–60 drops per min.

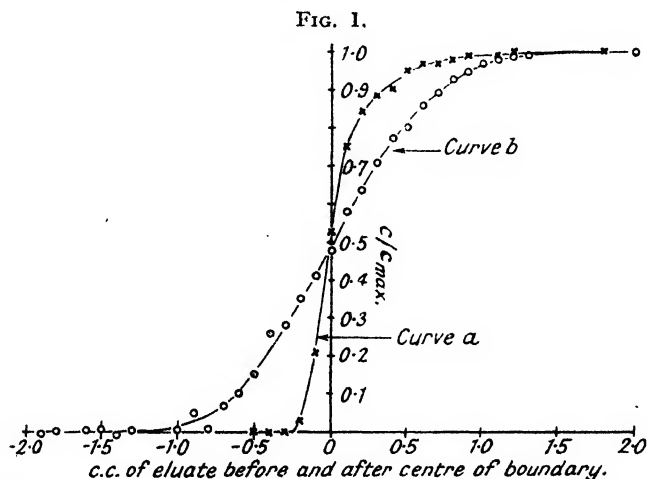
Systematic experiments showed that the quality and sharpness of non-sharpening inter-boundaries, e.g., such as between copper and manganese ions on Zeo-karb H.I. or H.I.P., continuously increased with reduction of grain size and flow rate. There must be an optimum flow rate, as the latter can obviously not be infinitely decreased without introducing disturbances on account of diffusion. But this latter effect is so small compared with the non-equilibrium effect and other disturbances that even at the lowest flow rates used an improvement was still noticeable compared with faster flow rates.

Under the conditions mentioned above ($d = 0.01$ mm., $F = 0.001$ cm./sec.), we were able to obtain, for a column of 1 m. length, non-sharpening inter-boundaries between 0.6 and 1 cm., and self-sharpening front boundaries extending on one occasion over only 0.10 cm., the former corresponding to 0.5–1%, the latter to 0.1% of the threshold volume.

That these conditions are not obtained with the usual practice can be seen from Fig. 10a of Weil-Malherbe (*J.*, 1943, 303), which contains about the best chromatographic experiments published. Here a non-sharpening front (benzpyrene on silica gel) extends over 25% of the threshold volume, and a strongly self-sharpening one (benzpyrene on alumina) over 12% of the threshold volume. A check on the form of non-sharpening front boundaries is therefore essential in all experimental work connected with the study of elution curves and, in particular, in such cases where elution curves are used for the calculation of adsorption equilibria (see Glueckauf, *Nature*, 1945, 156, 748, and Part II).

Although it is apparent that non-equilibrium phenomena can easily occur in the case of exchange materials, it is not usually realised that the same, though perhaps to a lesser degree, also applies to the so-called "adsorbents" like alumina and calcium carbonate, as adsorption takes place not only on the surface, but also inside the grains. The reason for this is that most experimenters investigating the form of bands have worked with single solutes which usually have strongly self-sharpening fronts. These maintain a reasonable sharpness even if considerably disturbed by non-equilibrium phenomena. Consequently, observers are easily deceived by this appearance of moderately sharp fronts, which are usually taken as proof of the absence of non-equilibrium phenomena.

How far the process of wishful thinking can go is shown, *e.g.*, by Jacobs and Tompkins (*Trans. Faraday Soc.*, 1945, **41**, 401, Fig. 1, Curve A), who convinced themselves—with the help of the equilibrium curve applied to a diffuse non-equilibrium boundary—that, in spite of the very diffuse eluted front which they found, the front of the adsorbate in the column



Experimentally measured boundaries. (a) Self-sharpening threshold boundary of $N-CoCl_2$ solution in column of acid Zeo-karb. ($\times - \times - \times$) (compare with curve calculated for $bc^0 = 10$ in Fig. 4). (b) Non-sharpening inter-boundary between frontal band of $^{59}CoCl_2$ and mixed band of $^{59}CoCl_2$ and $^{60}CoCl_2$ in same column of Zeo-karb ($\bigcirc - \bigcirc - \bigcirc$) (symmetrical S shape).

must have been very sharp. By doing so, they overlooked the fact that a sharp front of adsorbate moving through the column must deliver the solute at the end in an equally sharp-fronted elution curve—simply by reason of the conservation of matter (for details see eqn. 5).

The non-equilibrium phenomena, however, become very obvious when fronts are concerned which have little or no self-sharpening properties, *e.g.*, the boundary of one solute against another of similar adsorption affinity. As it is just such a boundary which occurs at the point of separation of two similar solutes (boundary EF in Fig. 1 of Part III), these non-equilibrium effects greatly reduce the efficiency of the separation.

(c) *Form of the Disturbed Self-sharpening Front Boundary.*—No theory has so far been given for the theoretical form of a front boundary disturbed by non-equilibrium phenomena in the case of a non-linear isotherm. Weiss (*J.*, 1943, 301; eqns. 59–62 and Fig. 5) has produced a schematical representation for the case of a linear isotherm which, however, apart from the diffuseness, does not really represent the experimental facts (see our Fig. 1, curve b, showing that the measured elution curve of a front boundary for a strictly linear isotherm has a symmetrical sigmoid form. A similar conclusion has also been reached by Klotz, *Chem. Rev.*, 1946, **39**, 243). A satisfactory theory for the case of the linear isotherm has been produced by Dr. H. London which, however, has not yet been published.

In the case of a self-sharpening front boundary caused by a non-linear isotherm, the general differential equations become very complicated, but, after the front has travelled some distance, a final form is attained which can be represented by a simple equation. Here the effects of non-equilibrium and self-sharpening just balance each other. For simplicity the calculations are carried out for the "undeveloped" chromatogram where the front has the original concentration c^0 .

In the case of non-equilibrium, the usual chromatographic equation of mass conservation (see Part II, eqn. 2), viz.,

$$[\Delta v/\Delta x]_e = df^*_{(e)}/dc + \alpha \quad (1)$$

changes to

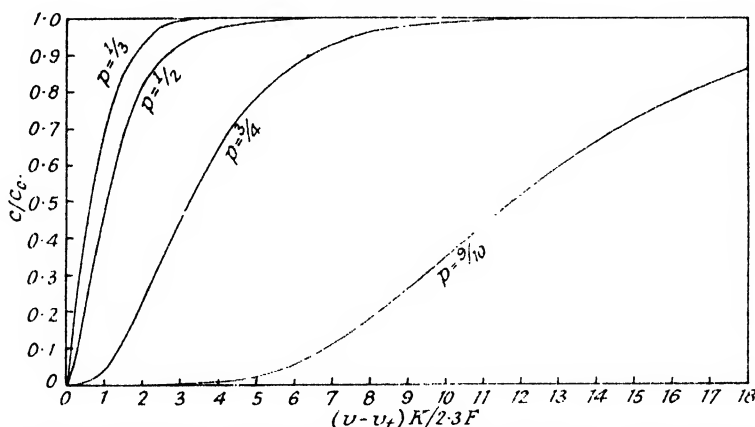
$$[\Delta v/\Delta x]_e = dq^*/dc + \alpha \quad (2)$$

where q^* is the amount actually adsorbed, the missing amount ($f^*_{(e)} - q^*$) being due to disequilibrium. When at a given point (x) of the front boundary the concentration rises during the passage of the front through this point, q^* is, with good approximation, represented by the equation

$$dq^*/dt = K(f^*_{(e)} - q^*) \quad (3)$$

which means that the rate of diffusion into the grains is essentially proportional to the amount still required to produce equilibrium. Here K is a diffusion factor (the inverse of the time in which a grain of adsorbent reaches $1/e$ of its equilibrium adsorption), and $K = D/(\eta d)^2$, where D is the diffusion constant of the solute in the solid material, d is the grain diameter, and $\eta (< 1/2)$ depends on the geometry of the grains.

FIG. 2.



Self-sharpening front boundaries for solutes obeying Freundlich isotherms $q = ac^p$ for different values of p .

After competition between the self-sharpening and the non-equilibrium effects has resulted in a final form of the front boundary, the whole front boundary and thus also the point of concentration c move with the usual velocity of the sharp undeveloped front boundary

$$[\Delta v/\Delta x]_e = f^*_{(e)}/c^0 + \alpha \quad (4)$$

It follows from equations (2) and (4) that in this final state

$$dq^*/dc = f^*_{(e)}/c^0 \quad (5)$$

This means that, no matter what the form of the equilibrium isotherm, q^* must always be a linear function of c . Eliminating q^* by means of (5) in (3) and replacing t by v/F (where F = flow velocity of solvent, in c.c./sec.), we get

$$dc/dv = (K/F)[f^*_{(e)} \cdot c^0/f^*_{(e)} - c] \quad (6)$$

Equation (6) has a particularly simple form in the case of the Freundlich isotherm

$$f^*_{(e)} = A \cdot c^p \quad (7)$$

Integration of (6) then leads to the equation for the elution curve of a disturbed self-sharpening front (final state):

$$v - v_t = \frac{-F}{K(1-p)} \cdot \log [1 - (c/c^0)^{(1-p)}] \quad (8)$$

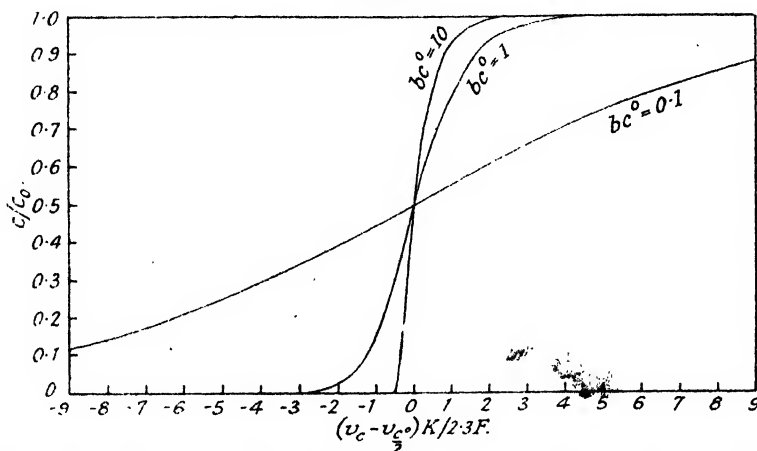
Similarly one obtains for the frontal distribution in the column

$$x_f - x = \frac{-F}{K(1-p)} \cdot \frac{c^0}{f^*_{(e)}} \cdot \log [1 - (q^*/q^0)^{(1-p)}] \quad (9)$$

where x_f is the most advanced point of the front boundary. Equation (8) requires that the length of the eluted front is independent of the concentration c^0 , which is perfectly shown in Jacobs and Tompkins's Fig. 2 (*loc. cit.*, p. 402). Equation (8) also shows the effect of p on the slope and extension of the front boundary, which is demonstrated in the experiments of Weil-Malherbe (*loc. cit.*, Fig. 10a), though not quantitatively, since, with the short columns used, the final state is not attained for values of p near unity.

Fig. 2 gives the theoretical curves of eluted front boundaries in the stationary state for various values of p . It shows that for small values of the Freundlich exponent p (e.g., $p = \frac{1}{2}$) the front rises sharply but reaches the maximum (c^0) only asymptotically. For comparatively large values of p it has a sigmoid form, which for $p = \sim 1$ reaches both the values $c = 0$ and $c = c^0$ asymptotically.

FIG. 3.



Self-sharpening front boundaries for solutes obeying Langmuir isotherm $q = ac/(1 + bc)$ for different values of bc^0 .

Equation (8) also shows that the question of grain size and flow rate comes into play to a very marked extent only when very similar substances have to be separated, where the inter-boundary is due to an exchange isotherm which, for very similar substances, is almost linear ($1 - p = \sim 0$; thus $v - v_c = \sim \infty$). No final state is attained by the front boundary when $p = 1$ (linear isotherm), under which conditions there is no self-sharpening effect, and, consequently, the slope of such a front boundary continues to decrease indefinitely.

Very similar conditions arise in the case of the Langmuir isotherm

$$f^*(c) = ac/(1 + bc) \quad (10)$$

Here integration of eqn. (6) leads to the equation for the elution curves :

$$v_c - v_c^0 = -\frac{K}{F} \left[\frac{1}{bc^0} \cdot \log (c^0 - c)/c + \log 2 (c^0 - c)/c^0 \right] \quad (11)$$

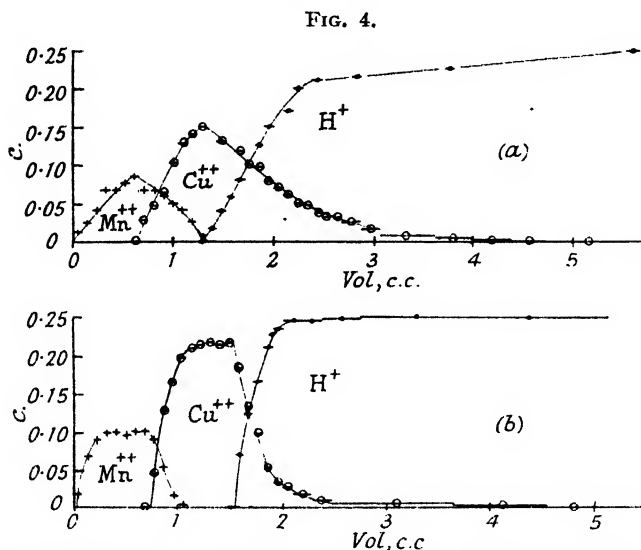
The form of the front boundary here depends on bc^0 which, according to the physical interpretation of the Langmuir isotherm, is the ratio of covered to free adsorbing surface. As can be seen from Fig. 3, the self-sharpening tendency increases with bc^0 , i.e., with increasing surface saturation. A comparison with Fig. 2 shows that there is a complete parallelism in the form of the front boundaries for the two isotherms, small values of p corresponding to large values of bc^0 and vice versa.

The diagrams of two accurately measured front boundaries are shown in Fig. 1. Curve *a* is the eluted front boundary of a 1N-[CoCl₂] band after passing 3g of acid permutite. The isotherm is approximately of the Langmuir type with a value of $b \approx 3-4$ (thus $bc^0 = 3-4$). A comparison with the corresponding calculated curves in Fig. 3 shows a good agreement. Curve *b* shows an inter-boundary between a mixture of ⁵⁹Co and ⁶⁰Co against a front-band of pure ⁵⁹Co, where the rise in the concentration of ⁶⁰Co has been measured. As the exchange isotherm between the two isotopes is strictly linear, there is no self-sharpening to be expected, and the experiment shows, in agreement with the theory, a symmetrical S-form for this front boundary.

The elution curve of the boundary of the two isotopes was measured by means of the β activity of ^{60}Co ($\tau = 5.5$ years) in single drops of eluate which were dried on filter-paper.

(d) *Effect of Non-equilibrium on Separation of Two Solutes.*—A typical example of the importance of such considerations is shown in the separation of copper and nickel on commercial alumina by Jacob and Tompkins (*loc. cit.*, p. 398, Fig. 3), using a linear flow velocity of 0.07 cm./sec. Even after the band has travelled several times the distance which they expect to be required for complete separation, the mixed part of the band still contains about 70% of the nickel and about 30% of the total copper.

We obtained very similar results with copper and manganese (the latter being used instead of nickel owing to its easy volumetric determination). Using a flow velocity of 0.027 cm./sec. and 0.25N-sulphuric acid for elution on 2.2 g. of commercial alumina, we obtained the elution curve of Fig. 4a, which shows the retention of a mixed band with 47% of the manganese and about 25% of the copper. (Figs. 4a and b were obtained by analysing single drops of eluate.)



Elution curves of mixture of CuSO_4 and MnSO_4 chromatographed on 2.2 g. of Al_2O_3 . Development with 0.25N- H_2SO_4 .

Abscissa : volume of eluate after appearance of solute in eluate.

Ordinate : concentration of solutes in eluate (milliequiv./c.c.).

(a) Diameter of $\text{Al}_2\text{O}_3 = 0.08$ mm.; flow velocity = 0.027 cm./sec.

(b) Diameter of $\text{Al}_2\text{O}_3 = 0.01$ mm.; flow velocity = 0.0014 cm./sec.

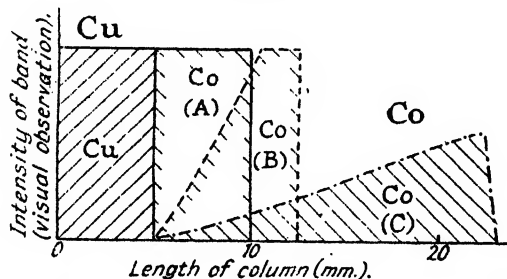
By reducing the grain size from 0.08 to 0.01 mm. diameter and the flow velocity to 0.0014 cm./sec., and otherwise using identical conditions, the effect of the diffusion and non-equilibrium phenomena was much reduced (see Fig. 4b). The mixed part of the band now contained only 20% of the manganese and 14% of the eluted copper, and in some experiments still less. (Actually, separation appeared to be much more complete in the column, and the small amount of mixing observed in the eluate seemed to be due to the mixing of 2 or 3 drops at the bottom of the tube.) Also, in other respects, the two experiments show marked differences. In the second experiment (Fig. 4b) all the front boundaries of the Mn^{++} , Cu^{++} , and H^+ are fairly steep, and the flat levels of the manganese and copper bands show clearly that these bands are not being "developed" by a diffuse rear boundary, a feature which is lost completely through non-equilibrium phenomena in Fig. 4a, and in the copper elution curves of Jacob and Tompkins (*loc. cit.*, p. 402, Fig. 2).

Although, under ordinary working conditions (commercial grain size and usual flow rate), some separation is still shown in cases where the differences in adsorption affinity and the self-sharpening tendencies of the inter-front are comparatively large, as is the case for Cu-Ni and Cu-Mn, it becomes impossible to separate solutes of very similar adsorption affinity, which consequently have fairly linear exchange isotherms, and whose inter-front is practically non-self-sharpening.

Such solutes as, *e.g.*, the group Ni, Co, Cd, Fe^{II}, are usually considered as non-separable (see Schwab and Jockers, *Z. angew. Chem.*, 1937, 50, 646), but their inseparability is entirely due to the disturbing influence of diffusion and non-equilibrium phenomena which almost completely undo any chromatographic separation. No difficulty is experienced in effecting an almost complete separation—with adjoining bands, of course—between any two of these solutes if a smaller grain size and a lower rate of flow is employed. To give an example: 0.15 c.c. of 0.5N-NiSO₄ + 0.5N-CoSO₄ were developed with 0.25N-H₂SO₄. The original band, in a column of alumina of 8 mm. diameter, had a length of 4.5 mm. The band at first broadened on development with the more dilute acid and, by the time the just visible rear band of nickel had travelled 6 mm., separation was complete, the nickel occupying a position between 6 and 12 mm., and the cobalt that from 12 to 18 mm. Treatment with dimethylglyoxime and ammonia showed that, if there were any overlap between the nickel and the cobalt zone, it must have been less than 1 mm. A quantity of 0.3 g. of alumina thus proved to be sufficient to separate almost quantitatively 0.15 milliequiv. of the "inseparable" cobalt-nickel sulphate mixture.

It should also be mentioned that, as a result of using finer grain, the quality of packing was much improved. The boundaries obtained were absolutely straight. Fringes—only observable under the microscope—did not exceed 3–4 grain diameters, *i.e.*, 0.04 mm. on any of the boundaries of Fig. 4b.

FIG. 5.



Chromatogram of mixture of CuSO₄ and CoSO₄ on Al₂O₃. Development with MnSO₄ solution. Cu band remains at the top of the column. Three stages in the "development" of the Co band are shown.

(e) *Separation into Isolated Bands.*—As the slow separation of metal ions on fine-grain alumina proved so successful, an attempt was made to obtain a complete separation into isolated bands. With acid as developing agent, this is of course not possible, as hydrogen ions are the most strongly adsorbed ions and, consequently, the bands cannot be expected to separate (see Glueckauf, Part I, *Proc. Roy. Soc.*, 1946, A, 186, 50, case 4). If a complete separation, *e.g.*, of copper and cobalt bands is required, development must be attempted with a less adsorbed solute, such as Mg⁺⁺ or Mn⁺⁺ solutions.

Fig. 5 shows the approximate distributions of the separated bands observed during a chromatographic separation of 0.15 c.c. of 0.5N-CuSO₄ + 0.5N-CoSO₄, developed with 1, 1.5, and 4.5 c.c. of 0.5N-MnSO₄ solution. Already after 1 c.c. of developing solvent had been added, the separation of copper and cobalt seemed almost complete, resulting in adjoining bands of about equal width. Further development hardly altered the position of the copper band. The front of the cobalt band continued to move down the column, but the tail end, though greatly decreasing in concentration, never moved away from the front of the copper band, a typical sign that cobalt ions follow a Freundlich isotherm even in the presence of 0.5N-Mn⁺⁺. (During the development it looked as if the bands were actually completely apart, but subsequent treatment with ammonium sulphide showed that the cobalt band reached right back to the copper front.)

Thus, if separation into two entirely separated bands were required, it would in this case be necessary either to develop with a solute of intermediate adsorption affinity (*e.g.*, zinc), or to add such a solute to the mixture and develop with acid.

Somewhat similar is the separation of nickel and cobalt with 0.5N-MnSO₄ solution as developing agent. Here both bands attained a triangular shape of approximately equal length, the nickel band beginning at the top of the column, and the cobalt band at the fairly sharp front of the nickel band. (The cobalt band was here not actually a triangle, but began

with a definite concentration, as must be expected for Freundlich isotherms. This is shown in detail in Figs. 4, 5, and 6 of Part V.)

Our thanks are due to Dr. H. London, University of Birmingham, who first drew our attention to the great importance of non-equilibrium phenomena for the separation of solutes of very similar adsorption affinity.

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[Received, November 26th, 1946.]

242. Theory of Chromatography. Part V. Separation of Two Solutes Following a Freundlich Isotherm.

By E. GLUECKAUF.

An attempt is made to predict the behaviour during chromatographic separation of solutes following individually a Freundlich isotherm $ac = q^n$. A method is shown for the graphical solution of the fundamental chromatographic equation $dq_1/dc_1 = dq_2/dc_2$, which makes it possible to calculate the distribution of solutes in binary chromatograms for any type of isotherm. It is shown that in the case of Freundlich isotherms two essentially different types of chromatogram must be expected (see Figs. 4 and 6). In order to obtain complete separability into two adjoining bands the condition must be fulfilled that the molar phase ratio at the point of separation of the bands

$$\left[\frac{q_2}{c_2} \cdot \frac{c_1}{q_1} \right]_0 > n_2$$

If the leading solute has the lower value of n , i.e., if $n_1 < n_2$, this can always be achieved by working at low enough concentrations. If this condition is not fulfilled, solute 2 cannot be obtained pure, but can only be enriched. Pure solute 1 can always be obtained, though in the latter case not quantitatively. Chromatographic separation is the easier the smaller the ratio n_1/n_2 of the Freundlich exponent.

(a) *An Isotherm for Multiple Solutes.*—The case of the Langmuir isotherm has been dealt with in considerable detail in an earlier publication. In deducing what happens in the case of two substances each following a Freundlich isotherm, the difficulty arises that no isotherm of the Freundlich type has so far been suggested for multiple solutes. Nevertheless, we may assume that, just as the simple Freundlich isotherm $q = (ac)^n$ can be replaced by a sum of Langmuir equations

$$q = \sum_1^n \frac{a_i c_i}{1 + b_i c_i} \quad \dots \quad (1)$$

as has been suggested by Hinshelwood ("Kinetics of Chemical Change in Gaseous Systems", 2nd edition, p. 195), the multiple Freundlich isotherm, if it existed, might be synthesised as

$$q_1 = \sum_1^n \frac{a_{1i} c_{1i}}{1 + b_{1i} c_{1i} + b_{2i} c_{2i}} \quad \dots \quad (2)$$

An isotherm of this type, which still has a finite slope (dq/dc) at $c_1 = 0$ would show little difference in principle from the chromatographic behaviour of a "pure" Langmuir isotherm, and such differences would be confined mainly to a smaller rate of separation at the rear end (see, e.g., Part III, Fig. 2).

Another possibility is to write the Freundlich equation in the form

$$ac = q(q)^{n-1} \quad \dots \quad (3)$$

and compare it with the Langmuir equation in the form

$$ac = q(1 - \beta q)^{-1} \quad \dots \quad (4)$$

where $\beta = b/a$ represents the amount of adsorbent occupied at saturation by 1 mol. of adsorbate. If the mechanism of adsorption is similar, we may reasonably assume that in both cases the concentration of the solute is in the first instance proportional to the concentration in the adsorbed state (q), modified by a factor which is dependent on the amount of free adsorbing space still available, which is a function of the amount absorbed. In the case of the multiple Langmuir isotherm this modifying function is

$$\left[1 - \beta_1 \left(q_1 + \frac{\beta_2}{\beta_1} q_2 \right) \right]^{-1}$$

We may assume that a similar additivity would exist for the occupied surface areas in the case of the modifying function of a multiple Freundlich isotherm, which would then have the form, analogous to eqn. (3) :

$$\left. \begin{aligned} a_1 c_1 &= q_1 \left(q_1 + \frac{\beta_2}{\beta_1} q_2 \right)^{n_1-1} \\ a_2 c_2 &= q_2 \left(\frac{\beta_1}{\beta_2} q_1 + q_2 \right)^{n_2-1} \end{aligned} \right\} \dots \dots \dots (5a, b)$$

Equation (5a, b), which, like the Freundlich equation, can only be considered as empirical, should make it possible to predict the conditions of mixed adsorption when the single-solute isotherms are known, at least if the surface requirements β can be considered identical.

Actually it is possible to make physical assumptions which link the Freundlich isotherm with the theoretically deduced Langmuir equation (though it cannot be discussed here how far these assumptions are justified). We may assume that every part of the surface can become an actively adsorbing spot, if raised temporarily to a higher energy level P which in this case corresponds to a state of unsaturation. The higher this degree of unsaturation, the larger must be the activation energy P , but the greater will be the amount of desorption energy Q which an adsorbed solute requires for its removal from this activated spot. The simplest assumption would be that P and Q form, at a given temperature, a definite ratio $P/Q = m$, where $m < 1$, so that activation + adsorption results in an exothermic process.

A Maxwell-Boltzmann distribution being assumed for the P levels, the proportion of active surface ΔS_Q adsorbing with an adsorption energy between Q and $Q + \Delta Q$ is

$$\frac{\Delta S_Q}{\Delta Q} = \frac{m}{RT} \cdot e^{-mQ/RT} \dots \dots \dots (a1)$$

There is no reason why in normal cases a group of active spots of uniform properties should not adsorb according to the Langmuir isotherm :

$$\Delta q_Q = \frac{\Delta S_Q}{\beta} \cdot \frac{Kc e^{Q/RT}}{(1 + Kc e^{Q/RT})} = \frac{\Delta S_Q}{\beta} \cdot \frac{b_Q c}{1 + b_Q c} \dots \dots \dots (a2)$$

Replacement of ΔS_Q in (a2) by means of (a1) and elimination of Q by b_Q leads to the equation

$$\Delta q_Q = \frac{m K^m c}{\beta \cdot b_Q^m (1 + b_Q c)} \cdot \Delta b_Q \dots \dots \dots (a3)$$

and integrating over all values of Q , i.e., for all adsorption factors b from 0 to ∞ , we have

$$q = \frac{m K^m c}{\beta} \int_0^\infty \frac{db}{b^m (1 + bc)} \dots \dots \dots (a4)$$

which for $0 < m < 1$ results in

$$q = \frac{m \pi K^m}{\beta \sin m\pi} \cdot c^m = A c^m \dots \dots \dots (a5)$$

This is the well-known form of the Freundlich isotherm.

The same considerations can be applied to the case of two solutes. This leads eventually to

$$q_1 = \frac{m_1 K_1^{m_1} c_1}{\beta_1} \int_0^\infty \frac{db_1}{b_1^{m_1} \left[1 + b_1 c_1 + \left(\frac{b_1}{K_1} \right)^{m_2/m_1} K_2 c_2 \right]} \dots \dots \dots (a6)$$

which integral appears to be soluble only for the case $m_1 = m_2$. In this case, integration leads to equations for q_1 and q_2 which are almost identical with the equations 5c, d. This gives some theoretical support for the multiple adsorption isotherms 5a, b, though only in the case $n_1 = n_2$.

Unfortunately, very few experimental data on mixed adsorption are available to test the usefulness of equation (5a, b), one of the best examples being the adsorption of oxalic (1) and succinic (2) acids on charcoal (probably by Masius; see Freundlich, "Colloid and Capillary Chemistry," Methuen, Fig. 39, p. 200). The Freundlich isotherms of the single solutes obtained from the experimental data are $40c_1 = (q_1)^{1.1}$ and $216c_2 = (q_2)^{2.6}$, where c is measured in mol./l. and q in millimol. per g. of charcoal, from which would follow in accordance with eqn. (5a, b), the multiple isotherms

$$40c_1 = q_1 \left(q_1 + \frac{\beta_2}{\beta_1} q_2 \right)^{1.1} \dots \dots \dots (5a')$$

$$216c_2 = q_2 \left(\frac{\beta_1}{\beta_2} q_1 + q_2 \right)^{2.6} \dots \dots \dots (5b')$$

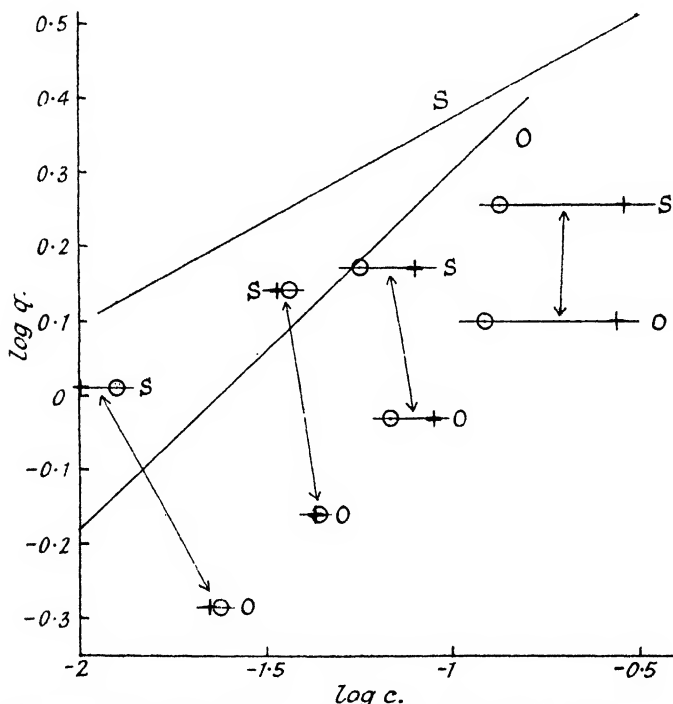
Fig. 1 shows the straight lines of the single-solute isotherms of succinic acid (S) and oxalic acid (O), as well as a number of points giving the measured adsorption equilibria for approximately

equimolar solutions of the mixed solutes, the points of coexisting concentrations being tied by arrows. From the values of q_1 and q_2 of these points the "theoretical" values of c_1 and c_2 have been calculated by means of eqns. (5a') and (5b'), and the resulting points are shown in Fig. 1 as circles: β_2/β_1 has been chosen as 1.2 which slightly improves the agreement as compared with the assumption of equal surface requirements. Though the deviations of the calculated values of c_1 and c_2 from the observed values are not negligible, it is apparent that the equations (5a') and (5b'), the constants of which are taken from the single-solute isotherm, express the conditions of mixed adsorption with reasonable approximation.

Much better is the agreement with the experimental values if we consider the effect of the total adsorbate on the molar phase ratio ξ obtained from eqns. (5a) and (5b) :

$$\xi = \frac{c_1/q_1}{c_2/q_2} = \frac{a_2}{a_1} \left(\frac{\beta_2}{\beta_1} \right)^{n_1-1} \cdot \left(\frac{\beta_1}{\beta_2} q_1 + q_2 \right)^{n_1-n_2} \quad \dots \quad (6)$$

FIG. 1.



Adsorption of succinic and oxalic acid on charcoal. The lines represent the adsorption of the single solutes; the points show the data of mixed adsorption of the two acids, coexisting concentrations being tied by arrows. (+) observed data, (○) calculated from single solute isotherms by eqn. (5a', b').

(see Fig. 2). Here the points correspond to the experimental values of c_1 , c_2 , q_1 , q_2 , and the line is obtained from eqn. (6) with $\beta_2/\beta_1 = 1.2$, and all the other constants are taken from the single-solute isotherms. ξ is the separation factor and its importance for the chromatographic separation is similar to that of the molar phase ratio of the gaseous and the liquid phase for fractional distillation. The agreement is so much better here because any effects of mutual attraction or repulsion between the different adsorbed solutes, e.g., due to the heat of mixing in the surface, which are not considered in eqn. (5a, b), are greatly reduced in ξ . This, too, has its parallel in the vapour pressures of binary liquids, where the agreement between theory and experiment is always better for the molar phase ratio than for the concentration-pressure curves.

Very similar conditions exist in the case of the binary adsorption of acetone (i) and acetic acid (ii) on charcoal. The single-solute isotherms are here (see experiments by Michaelis and Rona, *Biochem. Z.*, 1909, 15, 204—207)

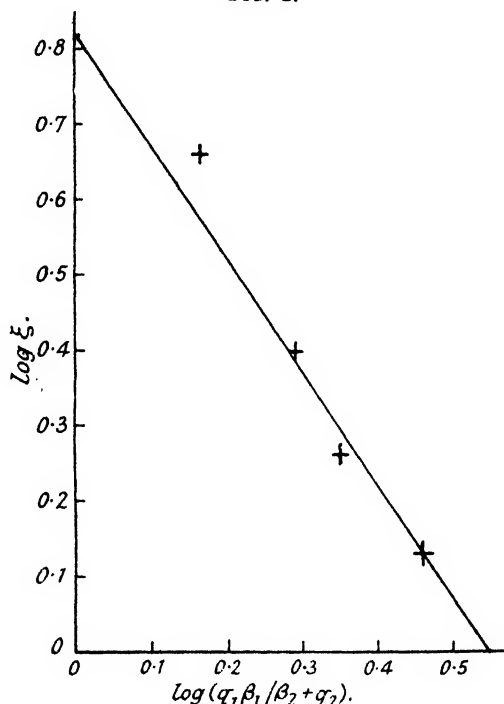
$$25c_1 = q_1^{2.0} \text{ and } 41.5c_2 = q_2^{3.0}$$

so that one might expect the multiple isotherms

$$25c_1 = q_1(q_1 + \epsilon q_2) \text{ and } 41.5c_2 = q_2 \left(\frac{q_1}{\epsilon} + q_2 \right)^2$$

At high concentrations of acetone, deviations due to the heat of mixing in the surface are again very marked, but at lower concentrations of acetone agreement is quite good (see Table I, where the concentrations in the solvent have been calculated for given quantities of adsorbate, using a value of $\epsilon = 0.65$), and Table II, where the amount of acetic acid required to produce a given distribution of

FIG. 2.



Mixed adsorption of succinic and oxalic acids. Molar phase ratio (ξ) plotted against mixed adsorption density according to eqn. (6).

TABLE I.

q_1 (milli-mol./g.).	q_2 (milli-mol./g.).	c_1 (mol./l.).		c_2 (mol./l.).	
		Calc.	Exp.	Calc.	Exp.
0.25	0.25	0.0041	0.0016	0.0024	0.0010
0.57	1.30	0.032	0.029	0.148	0.144
0.42	1.90	0.028	0.031	0.296	0.302
0.51	2.04	0.037	0.030	0.39	0.30
0.37	2.60	0.030	0.033	0.625	0.628

TABLE II.

Total acetone used (milli-mol.).	q_1 (milli-mol./g.).	c_1 (mol./l.).	Acetic acid added (milli-mol.).	
			Calc.	Exper.
0.209	0.043	0.0033	33.4	34.2
"	0.055	0.0031	13.9	17.1
"	0.061	0.0030	10.1	8.6
"	0.129	0.0016	0.4	0

solute 1 between 50 c.c. of water and 1 g. of charcoal has been calculated from the adsorption data of solute 1.

These considerations should make it clear that substances separately obeying a Freundlich isotherm do not necessarily follow the binary isotherm (5a, b), but that this equation represents

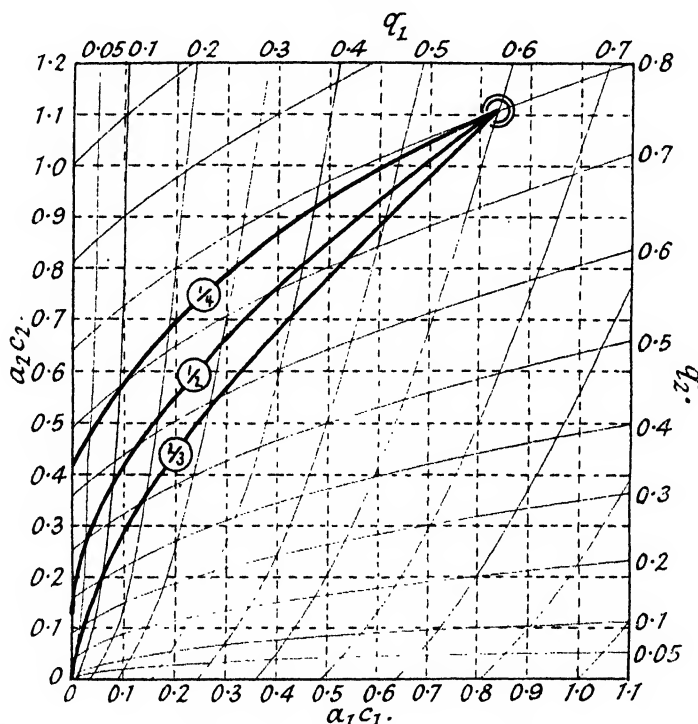
a function which contains many, though not necessarily all, the essential features, which may be expected from a multiple adsorption isotherm of such solutes. In particular, it contains the typical feature of the Freundlich isotherm of infinite slope at zero concentration.

For $n_1 = n_2$, $\beta_1 = \beta_2$. Eqn. (5a, b) can also be written in the form

$$\left. \begin{aligned} q_1 &= \frac{a_1 c_1}{(a_1 c_1 + a_2 c_2)^{1-1/n}} \\ q_2 &= \frac{a_2 c_2}{(a_1 c_1 + a_2 c_2)^{1-1/n}} \end{aligned} \right\} \quad \dots \dots \dots (5c, d)$$

which shows at the same time the formal resemblance to and also the essential difference from the multiple Langmuir isotherms.

FIG. 3.



Contour lines of the q_1 - c_1 - c_2 and of the q_2 - c_1 - c_2 surfaces, as required for obtaining the curve of coexistent values of c_1 and c_2 in the mixed part of the chromatogram for a given case of initial concentrations c_1^0 , c_2^0 (○). The three lines refer to three different values of a_1/a_2 ($= \frac{1}{4}$, $\frac{1}{2}$, and $\frac{3}{4}$).

(b) *Chromatographic Separation in the Case $n_1 = n_2$.*—In order to apply chromatographic equations to either eqn. (2) or (5), it is necessary to solve the fundamental differential equations governing the chromatographic process $dq_1/dc_1 = dq_2/dc_2$. As has been pointed out in Part I (*Proc. Roy. Soc., 1946, A, 186, 54*), a general solution is so far only possible in the case of the "pure" Langmuir isotherm. We can, however, solve this equation by graphical evaluation and thus obtain the relationships between coexistent values in the chromatogram of c_1 and c_2 or q_1 and q_2 in any numerical case.

For this purpose lines of equal q_1 and of equal q_2 are plotted on a system with the co-ordinates $a_1 c_1$ and $a_2 c_2$ (or c_1 and c_2) (see Fig. 3). These represent the contour lines of the three-dimensional q_1 - $a_1 c_1$ - $a_2 c_2$ and q_2 - $a_1 c_1$ - $a_2 c_2$ diagrams. We may then start with a point [representing the conditions of the original solution (c_1^0 , c_2^0) to be chromatographed] and, by a method of trial and error, find a neighbouring point which obeys the condition $\Delta q_1/\Delta c_1 = \Delta q_2/\Delta c_2$. Thence we proceed from point to point until one of the concentrations becomes zero. The resulting curve (thickly marked in Fig. 3) then represents the relationships between coexistent values in the mixed chromatogram of q_1 and q_2 , c_1 and c_2 .

In order to make a wider use of this diagram the evaluation has been made for three different values of a_1/a_2 ($= \frac{1}{2}, \frac{1}{3}, \frac{1}{4}$) which thus represent three different isotherms of the same type. The contour lines of Fig. 3 have been calculated for eqn. (5a, b) with $n_1 = n_2 = 2$ and $\beta_1/\beta_2 = 1$. In this case the position of the "coexistence line" depends on the ratio a_1/a_2 only, so no individual values need be assigned to these constants.

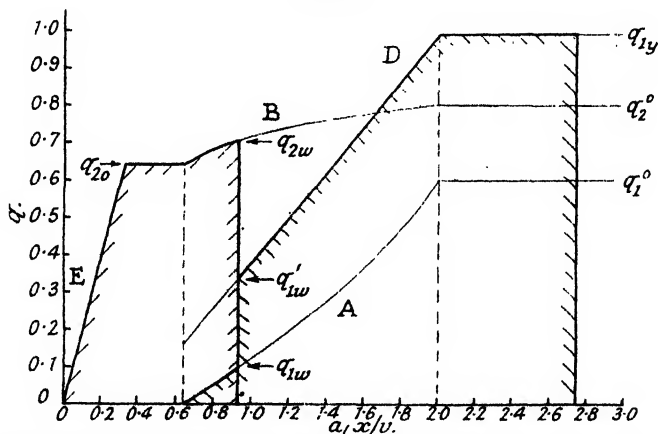
The starting concentrations of the adsorbate q_1^0 and q_2^0 have been chosen at random ($q_1^0 = 0.6$, $q_2^0 = 0.8$) and consequently $c_1^0 = 0.84/a_1$, $c_2^0 = 0.12/a_2$.

Each case of a_1/a_2 results in a function of coexistent values of c_1 and c_2 (and of q_1 and q_2 , respectively) and these functions differ greatly in their characteristics. It can be shown that different starting points c_1^0 , c_2^0 , q_1^0 , q_2^0 do not affect these characteristics, but that these depend on the ratio a_1/a_2 only. We always get types of function for coexistent values which can be represented with good approximation by the empirical equations (6a), (6b) and (6c), the value of the constants depending on the starting point.

a_1/a_2	Equations for coexistent values of q_1, q_2	Constants for $q_1^0 = 0.6$, $q_2^0 = 0.8$		
		k_1	k_2	k_3
$\frac{1}{2}$	$q_2 = k_1 + k_2 q_1 + k_3 q_1^2$	0.64	0.5	0.5 (6a)
$\frac{1}{3}$	$q_2 = k_1 + k_2 \sqrt{q_1}$	0.37	0.55	— (6b)
$\frac{1}{4}$	$q_2 = k_1^2 \sqrt{q_1} + k_2 q_1$	0.77	0.25	— (6c)

These relationships for coexistent values of q_1 and q_2 make it possible to substitute q_2 in the mixed isotherm (5a, b). This leads to the "pseudo-single-solute" isotherm $q_1 = F(c_1)$ required for the construction of the binary chromatograms according to the general equations given in Part III.

FIG. 4.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ and mixed $a_1/a_2 = \frac{1}{2}$. Note similarity with the case of the Langmuir isotherm. Complete separation is attainable.

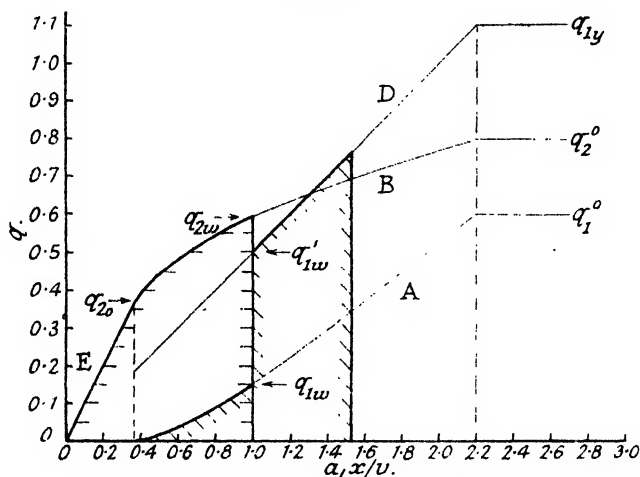
Figs. 4, 5, and 6 show the calculated loci of the chromatographic boundaries for the three cases considered ($a_1/a_2 = \frac{1}{2}, \frac{1}{3}, \frac{1}{4}$). Curves A and B represent the loci of the rear boundary of the mixed band for solute I and II respectively; curve D shows the rear slope of the pure frontal band of solute I, and curve E gives the diffuse rear boundary of the pure rear band of solute II. All the curves show the values of q_1 or q_2 plotted against the parameter a_1x/v as abscissa.

From these curves the actual form of the chromatograms can be obtained by fixing numerical values for the quantities of solutes (m_1, m_2) and for the volume v of solvent used. This defines the position x of the front boundaries of the mixed band and of the pure band of solute I. To make things clearer, these boundaries (for given cases of m and v) have been cross hatched; with these boundaries the abscissa represents the length of column (x) in an arbitrary unit.

We then see from Fig. 4 that, for solutes with values of $a_1/a_2 < \frac{1}{2}$, the general arrangement of the binary chromatogram shows little difference from that arising from a Langmuir isotherm (see Part I or Part III, Figs. 1a-e, Fig. 1A, B). The principal differences are that (a) the rear band does not separate from the top of the column, a known feature for Freundlich isotherms (see Weiss, *loc. cit.*, Fig. 4), and consequently is only very incompletely eluted, and (b) the

frontal band of solute 1 never completely separates from the rear band of solute 2, even after the mixed band has disappeared, because on account of the infinite value of dq/dc at $c_1 = 0$, the tail of the frontal band moves infinitely slowly and thus would always be overtaken by any other substance with $c > 0$ (see Fig. 5 of Part IV). The complete separation into two distinct bands

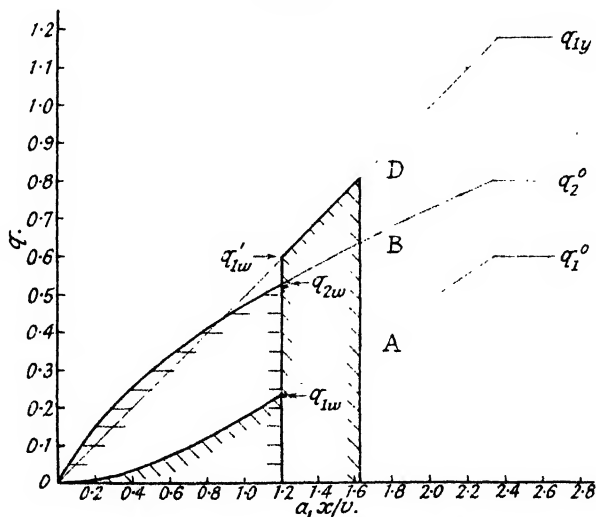
FIG. 5.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ and $a_1/a_2 = \frac{1}{2}$. Intermediate case between Figs. 4 and 6.

of two solutes can therefore always be taken as a sign that the strict Freundlich isotherm does not apply to the faster-moving solute at very low concentrations, but that a pseudo-Freundlich isotherm of the type of eqn. (1) applies, which, as has been shown by a similar diagrammatic investigation, always permits separation into two distinct bands.

FIG. 6.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ and $a_1/a_2 = \frac{1}{3}$. Note that no pure solute II is separable; consequently no complete separation is attainable.

This conclusion agrees with the experimental findings by Schwab and Jockers (*Z. angew. Chem.*, 1937, 50, 646) that no white zones between coloured bands can be obtained when mixed inorganic solutes are chromatographed on alumina, where isotherms with Freundlich characteristics obtain.

The difference of the chromatograms from those of Langmuir isotherms becomes marked for small separability of the two solutes ($1 > q_1/q_2 > 0.5$) (see Fig. 6). Here the flat portion at the front of the pure tail band of solute II and the discontinuity at this point disappear. On the other hand, there is no longer a point of complete separation, as the curve representing q_1 now runs right back to the top of the chromatographic column ($x = 0$). In this case, solute II cannot even partially be obtained in the pure state, though a certain amount of solute I can be obtained pure at the front boundary.

Between these two extremes lies the intermediate case, $a_1/a_2 = \frac{1}{2}$ (see Fig. 5). Here we have the very rare, and in practice never realised case where a pure rear band can form without a discontinuity at its forward boundary, and where, consequently, the equations (in particular 6 and 7) suggested by Offord and Weiss (*Nature*, 1945, 155, 725), which do not normally hold good, become identical with those of Glueckauf (*ibid.*, 156, 205).

(c) *The Case of $n_1 \neq n_2$.*—It can be shown by a graphical integration (as in Fig. 3) that the two types of chromatographic behaviour as shown in Figs. 4 and 6 will also occur if $n_1 \neq n_2$. As in the case shown in Fig. 4, separation of a pure rear band of solute 2 (with a discontinuity at x_0) is confined to the essential conditions

$$\left[\frac{dc_1}{dq_1} \right]_{q_1=0} > 0 \quad \text{and} \quad \left[\frac{dq_1}{dq_2} \right]_{q_1=0} > 0 \quad . \quad . \quad . \quad (7)$$

This gives the possibility of discussing, not only the case of the isotherm (5a, b), but also the general isotherm of the type

$$c_1 = q_1 \phi(q_1, q_2) \quad c_2 = q_2 \psi(a_1 q_1, a_2 q_2) \quad . \quad . \quad . \quad (8a, b)$$

where ϕ and ψ are any functions, the latter being a symmetrical function with respect to $\alpha_1 q_1$ and $\alpha_2 q_2$. Then

$$\left[\frac{dc_1}{dq_1} \right]_{q_1=0} = \phi(0, q_2) \quad . \quad . \quad . \quad (9)$$

$$\left[\frac{dc_2}{dq_2} \right]_{q_1=0} = \psi(0, q_2) + q_2 \left[\frac{d\psi}{dq_2} \right]_{q_1=0} \quad . \quad . \quad . \quad (10)$$

Equating (9) and (10) results in

$$\left[\frac{c_1}{q_1} \cdot \frac{q_2}{c_2} \right]_{q_1=0} = \xi_0 = 1 + \frac{q_2 \phi^2}{c_2 \psi} \left[\frac{d\psi}{dq_2} \right]_{q_1=0} \quad (11)$$

which, after partial differentiation, leads to

$$\left[\frac{dq_1}{dq_2} \right]_{q_1=0} = \left(\xi_0 - \left[\frac{\partial \log c_2}{\partial \log q_2} \right]_{q_1=0} \right) / \frac{a_1}{a_2} \left(\left[\frac{\partial \log c_2}{\partial \log q_2} \right]_{q_1=0} - 1 \right) \quad (12)$$

As $dq_1/dq_2 > 0$, the condition for complete separability of the solutes is

$$\xi_0 > \left[\frac{\partial \log c_2}{\partial \log q_2} \right]_{q_1=0} \quad (13)$$

A useful application of (12) and (13) will in general be prevented by lack of knowledge of the value of q_{20} . But in the case of the isotherm (5a, b), $[\partial \log c_2 / \partial \log q_2]_{q_1=0}$ is independent of q_{20} and results in

$$\left[\frac{dq_1}{dq_2} \right]_{q_1=0} = a_2(\xi_0 - n_2)/a_1(n_2 - 1) \quad . \quad . \quad . \quad (12a)$$

and in the condition

$$\xi_0 > n_2 > 1 \quad . \quad . \quad . \quad (13a)$$

If, as in the case of Fig. 3, $n_1 = n_2$, ξ_0 has the simple value a_2/a_1 .

For a mixed adsorption isotherm of the type (5a, b) $\log \xi$ is a linear function of $\log \left(\frac{\beta_1}{\beta_2} q_1 + q_2 \right)$, and we can have two different cases, according to whether n_1 (less adsorbed solute) is smaller or larger than n_2 (rear solute). In the first case when $n_1 < n_2$ (or more generally, when ξ increases with decreasing concentration) the condition $\xi_0 > n_2$ is always fulfilled, as development can be continued until ξ is large enough (see Fig. 7a). The separation will be the more efficient the smaller $(q_1^0 + q_2^0)$, as this results in larger values of ξ^0 and ξ_0 . This case behaves thus quite differently from that of the Langmuir isotherm, where separation is accelerated by working at high adsorption densities.

For the second case, when $n_1 > n_2$ (or more generally, when ξ decreases with diminishing concentration) (see Fig. 7b), it is apparent that the separation, which increases with ξ , improves with increasing concentrations of the solutes. If, however, they are not high enough to result in a value of $\xi_0 > n_2$ (or more generally $\xi_0 > \left[\frac{\partial \log c_2}{\partial \log q_2} \right]_{q_1=0}$), which is essential for a clean separation of the solutes, the lowering of the concentrations in the course of the development will result in values of $\xi < 1$, at first for the rear, and eventually also for the front of the band. Thus, in the beginning, solute 1 will separate both in the front and in the rear with enrichment of solute 2 in the middle section of the band. Then, as the concentrations fall in the course of development, separation of solute 1 at the front will come to an end ($\xi_w = 1$) and will even be reversed ($\xi_w < 1$), whereby solute 2 again enters into the pure frontal band of solute 1 and eventually forms a frontal band of pure solute 2.

In this case, it is obviously much more economical to work from the start at such low concentrations that ξ^0 becomes < 1 . This means that the solutes change their subscript and order in the chromatogram, reverting thereby to the case shown in Fig. 7a. It follows from this that chromatography at low enough concentrations will always lead to some kind of separation or enrichment in the case of Freundlich isotherms, though, if $n_1 > n_2$, chromatographic separation at high concentrations may in some cases ($\xi^0 \gg n_2$) result in a faster and more efficient separation,

FIG. 7 a.

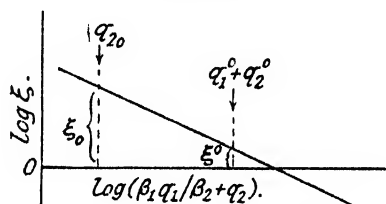
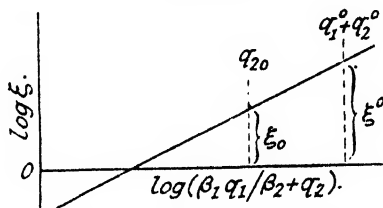


FIG. 7 b.



The separation factor ξ as function of the adsorption density. (a) $n_1 < n_2$: separation improves with the use of lower concentrations. (b) $n_1 > n_2$: separation improves with increasing concentration of the solutes.

particularly, when $c_1^0 \ll c_2^0$, which would result in a relatively large value of c_{20} and hence also of ξ_0 (of same order of magnitude as c_2^0 and ξ^0 respectively; this follows strictly for the Langmuir isotherm, and can be shown to be true for other isotherms by the graphical method).

The first of these conclusions is confirmed by the chromatographic practice, where low concentrations are generally favoured. The second case, where high concentrations improve the separation, and which has apparently so far not been looked for, will be investigated experimentally in due course.

It is also apparent from Fig. 7a and b that, if ξ^0 is identical for two pairs of solutes, where one has $n_1 < n_2$, and the other $n_1 > n_2$, separation will be far easier in the first case where the leading solute has the lower value of n , since during the process of development the value of ξ increases, while the converse is true if the leading solute has the higher n . More generally, it can be said that pairs of solutes with equal ξ can be separated the more easily the smaller the value of n_1/n_2 .

These conclusions might be elaborated more quantitatively, if the proposed binary isotherm (5a, b) were more than a rough working model which, apart from the displacement effect, does not consider mutual influences on each other of the two solutes. The present state of our knowledge concerning binary adsorption isotherms, however, is such that much preliminary work must be directed towards establishing the mutual influence of adsorbed solutes on each other and the mathematical form of mixed isotherms, before further theoretical guidance can be given to the practical chromatographer.

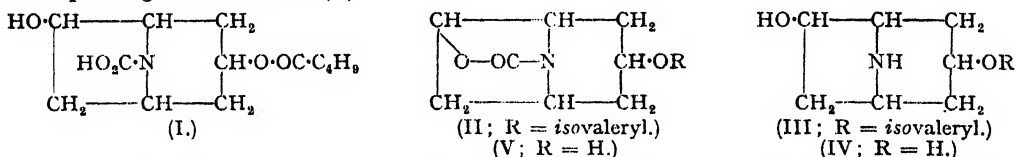
243. The Minor Alkaloids of Duboisia myoporoides. Part IV. Valeroidine.

By WILLIAM MITCHELL and E. M. TRAUTNER.

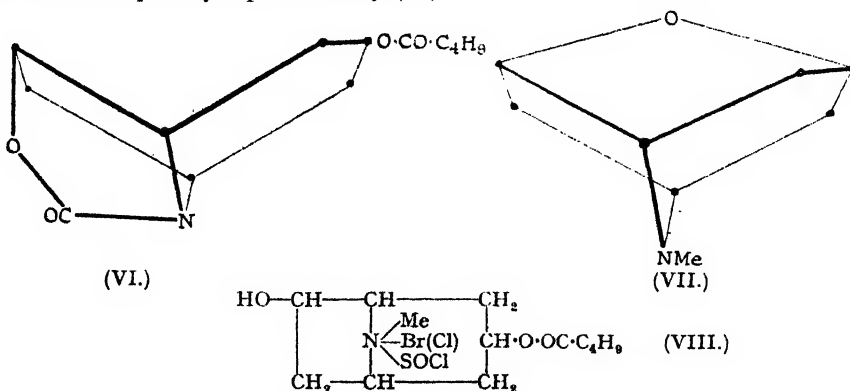
A final structure for valeroidine (*J.*, 1937, 1821; 1940, 1155) is proposed. The product of oxidation with permanganate in acetone is suggested to be an inner urethane, explaining the formation of norvaleroidine on acid hydrolysis. An explanation of the demethylating action of thionyl chloride on valeroidine hydrobromide is also proposed.

VALEROIDINE has been shown (Part I, *J.*, 1937, 1821) to be a monoisovaleryl dihydroxytropane. The parent tropanediol differed from the known 2:3- and 6:7-diols but was shown to be identical with the "dioxytropane" isolated from Peruvian coca leaves by Wolfes and Hromatka (*Merck's Jahresber.*, 1933, 47, 45) and which they suggested to be tropane-3:6-diol. In further work (Part III, *J.*, 1940, 1155) the diacetyl and diisovaleryl derivatives of the tropanediol were prepared and attempts were made to determine the positions of the free and esterified hydroxyl groups in valeroidine. Oxidation with various reagents in acid aqueous solution gave no positive results, but with potassium permanganate in acetone, besides a small yield of norvaleroidine [compare preparation of nortropine from tropine (Willstätter, *Ber.*, 1896, 29, 1580), norscopoline from scopoline (Lubold, *Arch. Pharm.*, 1898, 236, 22), etc.], a new neutral compound was obtained. At that time analysis indicated the formula $C_{13}H_{21}O_4N$ for this compound. On boiling with alcoholic hydrochloric acid the compound was converted into norvaleroidine. This was an unexpected result which could not then be explained.

It is now suggested that the oxidation product is an inner urethane (II) formed by elimination of water from a labile carbamic acid (I) initially produced by oxidation of the *N*-methyl group. Formula (II) requires $C_{13}H_{19}O_4N$, with which later analyses were in closer agreement; it would explain the formation of norvaleroidine (III) by elimination of carbon dioxide on acid hydrolysis. It is probable that the rather ill-defined base obtained, along with isovaleric acid, on alkaline hydrolysis of the oxidation product was a mixture of nortropane-3:6-diol (IV) and the corresponding inner urethane (V).



By analogy with hyoscyamine, hyoscine, etc., it is reasonable to assume that the esterified hydroxyl group is in position 3. On this assumption the comparative stability of the oxidation compound would appear to exclude the possibility that the free hydroxyl group in valeroidine could be attached to carbon 1 (or 5) since this would require the presence of a four-membered urethane ring in the oxidation product. The fairly ready formation of the latter would rather suggest that the free hydroxyl group was attached to carbon 6 (or 7), so that the oxidation product would be spatially represented by (VI).



Wolfes and Hromatka (*loc. cit.*) obtained a 73% yield of "tropene oxide", in which they postulated the presence of an ether linkage, by treating their tropanediol with a mixture of

phosphorus oxychloride and pentachloride. This compound, more correctly termed desoxy-scopoline, can be spatially represented by (VII).

In Part III (*loc. cit.*) attempts to replace the free hydroxyl group in valeroidine by chlorine were also described. These were unsuccessful, but on treating valeroidine hydrobromide (the free base did not give the reaction) with thionyl chloride the curious fact was noted that norvaleroidine was obtained in good yield. It is now suggested that this reaction proceeds through the formation of a labile compound (VIII) which, by loss of methyl chloride (or bromide) and subsequent hydrolysis, yields norvaleroidine (III).

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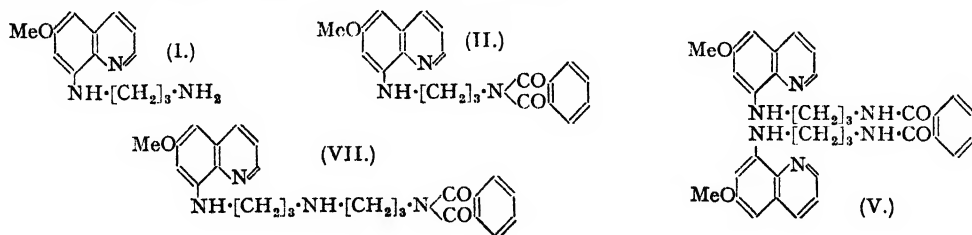
[Received, November 18th, 1946.]

244. Contributions to the Chemistry of Synthetic Antimalarials. Part IV. Hydrazine Hydrolysis and Radical Exchange Reactions of N-Substituted Phthalimides in Relation to the Constitution of the Antimalarial R.63.

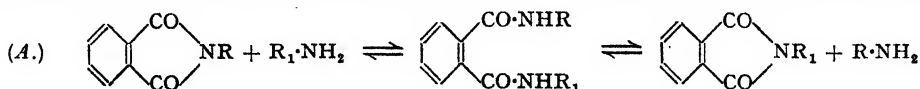
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Hydrazine hydrolysis of N-substituted phthalimides has been shown to give the *phthalylhydrazide* salts of the liberated primary amines. Facile radical exchange reactions have been observed between N-substituted phthalimides and substituted aliphatic primary amines. The special case of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II) has been studied in detail. The bearing of these reactions on the composition of R.63 is discussed. The antimalarial activity of R.63 can be accounted for on the basis of the 8-γ-aminopropylamino-6-methoxyquinoline (I) dihydrochloride it contains.

EARLY in 1944, we required 8-γ-aminopropylamino-6-methoxyquinoline (I) in quantity for part of our antimalarial research programme. In preparing this, we encountered certain side reactions relevant to the constitution of the synthetic antimalarial known as R.63 (Robinson and Tomlinson, *J.*, 1934, 1524). This subject had just been reopened by Robinson and his collaborators (*J.*, 1943, 555, 557, 561), who showed that the original constitution ascribed to R.63 was untenable and that most of the feasible alternatives were also excluded. Here was a synthetic drug of confirmed high antimalarial activity (Index 1/64) but of unknown constitution. The hypothesis that the activity was due to the presence, as an impurity, of a small proportion of a still more highly potent antimalarial was an attractive one. The discovery of the side reactions referred to above encouraged this view and indicated the nature of the impurities which might be expected. While our results do not provide absolute proof of the complete composition of R.63 and the source of its activity, they afford strong circumstantial evidence that it is a mixture of a number of products in which the dihydrochloride of (I) is present in sufficient quantity to account for the biological results obtained.



In the synthesis of "antimalarial side chains" by phthalimido-alkylation reactions with substituted aliphatic amines, the following scheme of facile radical exchange has been established:

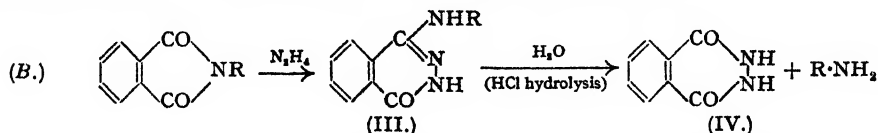


The main factors which determine the end products will be the electronic characteristics of R and R₁, and such relevant properties of their derivatives as solubility in the reagents used or

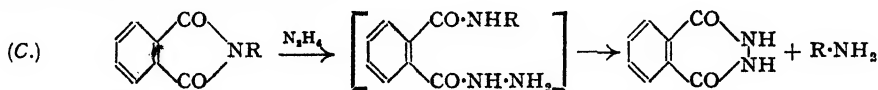
volatility at the reaction temperature. Examples of (A) where R and R₁ = Me, Et, or H have been described recently by Spring and Woods (*J.*, 1945, 625).

The importance to R.63 of the scheme (A) first became apparent while studying the hydrazine hydrate hydrolysis of 8- γ -phthalimidopropylamino-6-methoxyquinoline (II).

A number of workers (Baldwin, *J.*, 1929, 2962; Magidson and Bobishev, *J. Gen. Chem. Russia*, 1938, 8, 912; Beer, *ibid.*, 1939, 9, 2158; Quin and Robinson *J.*, 1943, 555) had previously used this reaction to prepare (I), their method being based on that of Ing and Manske (*J.*, 1926, 2349) who formulated the hydrolysis as follows:



We have found that the sparingly soluble intermediate which separates from the reaction mixture has not the structure (III) ascribed to it tentatively by Ing and Manske, but is in fact the salt of the acidic phthalylhydrazide (IV) with the liberated amine. It is more probable that the course of the reaction is:



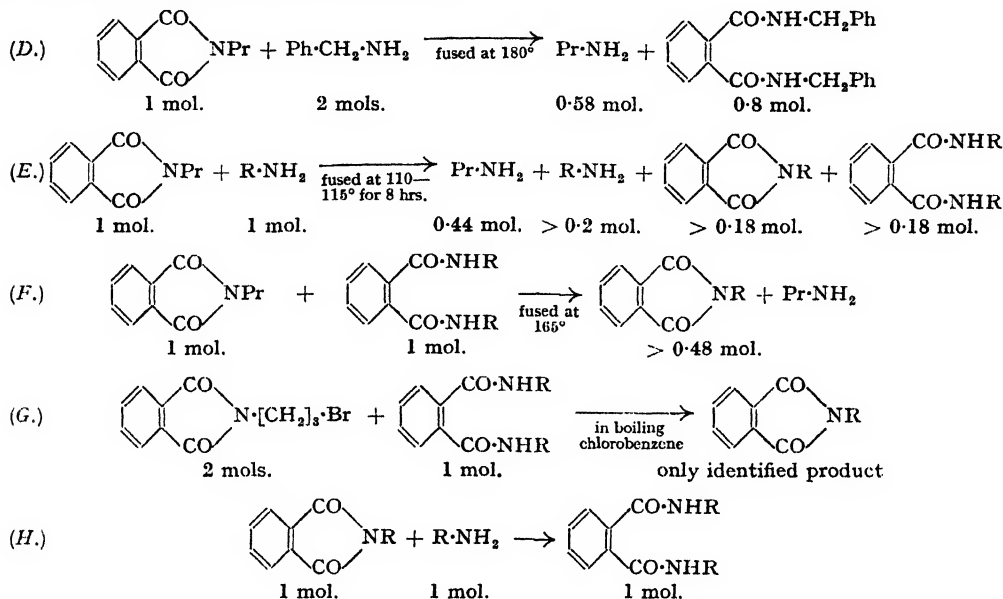
It is clear that this revised conception of the nature of the intermediate (III) suggests modified methods of isolating amines produced by the hydrazine reaction and thus broadens the scope of the method. It is no longer correct to regard the final stage of warming with acid as a hydrolysis of an intermediate such as (III), but as the simple decomposition of a salt by acid. This decomposition can also be effected by alkali, by solvent extraction, or by thermal dissociation. Incidentally, the last procedure provides a ready method of obtaining anhydrous volatile amines where their isolation from the aqueous solutions normally obtained is a matter of some difficulty; application to the laboratory preparation of anhydrous hydrazine will be recorded in a future note.

The intermediate salt we obtained by hydrazine hydrolysis of (II) was dissociated into its components by chloroform extraction and by basification. It was always contaminated by a proportion (dependent on the molar proportion of hydrazine, see Table I) of a secondary product, *phthalobis-[\gamma-(6-methoxy-8-quinolylamino)propyl]amide* (V). This arose by interaction [scheme (A)] between unchanged (II) and free primary amine (I), derived from the partial dissociation in the reaction mixture of its phthalylhydrazide salt. We have studied the acid hydrolysis of the phthalamide (V) under various conditions (Table II) to ascertain the fate of this impurity at the final stage of the Ing and Manske hydrolysis. Under typical conditions complete conversion into an equimolar mixture of (I) and (II) occurred. Thus in a hydrolysis of 1.0 mol. of (II) by the method of scheme (B) using 1.0 mol. of hydrazine hydrate, it can be deduced from Tables I and II that the only impurity present in the reaction product would be approximately 0.075 mol. of the phthalimide (II). This would be removed, together with the phthalylhydrazide, from the aqueous solution of the hydrochloride of the product (I) in the normal course of working up the reaction. The formation of the secondary product (V) can be eliminated by treating (II), dissolved in chloroform-alcohol, with two molar proportions of hydrazine hydrate at room temperature; (I) is then the only product obtained.

We next demonstrated the ready formation of the phthalamide (V) directly from (I) and (II), both in boiling alcohol and by fusion. The facile nature of these changes suggested that similar considerations would apply to the fusion of 8- γ -aminopropylamino-6-methoxyquinoline (I) and phthalo- γ -bromopropylimide—the first stage in the synthesis of R.63. Model experiments with some phthalimides and amines, selected for readier separation of the reaction products, confirmed scheme (A). These experiments are summarised in the following schemes in which R = γ -(6-methoxyquinolyl-8-amino)propyl.

Clearly in the first stage of the preparation of R.63, where phthalo- γ -bromopropylimide (VI) is substituted for phthalo-*n*-propylimide in equation (E), the products of the reaction may be very complex and their separation has proved extremely difficult. The yields of isolated and purified substances must therefore represent much less than the quantities formed in the reaction. From the product of fusing (I) and (VI) by the method of Glen and Robinson (*J.*, 1943, 557) we isolated in a pure state the following: 8- γ -phthalimidopropylamino-6-methoxyquinoline

(II) in 5% of the theoretical quantity, 8- γ -aminopropylamino-6-methoxyquinoline (I) in 10% recovery, and a small quantity of 8- γ -phthalimidopropyl- γ -aminopropylamino-6-methoxyquinoline (VII) monohydrobromide. Since our object was to identify the highly active component responsible *ex hypothesi* for the activity of R.63, we did not attempt quantitative separation of the mixture but turned our attention instead to the synthesis of compounds deduced from the application of scheme (A).



(II) doubtless appeared as the result of a reaction, type (E), from which we inferred that the highly reactive bifunctional compound, γ -bromopropylamine (VIII), was liberated simultaneously with (II). (VIII) could undergo self-condensation to 1:5-diazacyclooctane dihydrobromide (IX) or react in many ways with the various components of the melt. However, both the hydrobromide of (VIII) (Gabriel, *Ber.*, 1888, **21**, 2669) and (IX) (Buhle, Moore, and Wiselogle, *J. Amer. Chem. Soc.*, 1943, **65**, 29) have been found devoid of antimalarial activity.

As molecular proportions of the reagents (I) and (VI) are used in this fusion, the recovery of 10% of unchanged (I) indicated that a similar quantity of phthaloyl- γ -bromopropylamide (VI) might remain unchanged in the fusion product. This would react during the second stage of the preparation of R.63 (treatment of the crude fusion melt with alcoholic hydrazine hydrate followed by warm dilute hydrochloric acid) giving a variety of products. Accordingly, pure (VI) was submitted to the sequence of hydrazine treatment (using various molar proportions of hydrazine) and acid "hydrolysis", but the total basic product derived was always inactive.

Lastly the identification of the "normal" product (VII) of the fusion reaction of (I) and (VI) in the crude melt indicated that some 8- γ -aminopropyl- γ -aminopropylamino-6-methoxyquinoline trihydrochloride would appear in R.63.

Being impressed by the fact that most of the physical change in the fusion reaction took place during the first few minutes, we studied the rate at which the free amino-group of (I) reacted. Table III summarises the results of some Van Slyke nitrogen determinations and shows their relation to the quantities of the various products proved to be present in the melt after various times of fusion. It is noteworthy that the proportion of primary amine (Van Slyke) drops to approximately 30% of its initial value in the first five minutes of fusion and remains at this value even after the seven hours specified by Glen and Robinson (*loc. cit.*).

The complex nature of the first reaction in the preparation of R.63 made it apparent that alcoholic hydrazine hydrate treatment of the crude product could only add to its complexity. We did not therefore proceed to attempt to separate R.63 into its components. However, on the evidence submitted here R.63 would obviously contain at least 10% of unchanged (I), together with a further proportion of (I) (> 5%) formed when the phthalimide (II) present in the melt was treated with hydrazine hydrate. If the Van Slyke figure for N were taken as a

measure of the amine (I) present in the fusion product, a reasonable assumption, then the final R.63 could be calculated to contain > 35% of the possible quantity of the amine (I).

Results obtained in the Biological Laboratories, May & Baker Ltd., indicate that the antimalarial activity and toxicity of R.63 are in general accord with the chemical evidence that upwards of 30% of (I) is present. It should be emphasised, however, that extreme caution is necessary in interpreting the results obtained on a mixture, since the biological properties may be far from additive. The presence of a small proportion of a highly active substance is still not definitely excluded. A fuller discussion of the biological results will appear elsewhere in due course, together with a report on the antimalarial evaluation of phthalobis- $[\gamma$ -(6-methoxy-8-quinolylamino)propyl]amide (V) and 8- γ -phthalamidopropylamino-6-methoxyquinoline.

Addendum.—Publication of this work has been delayed largely because British Patent Application 17071/44, covering the preparation of the phthalamide (V), was placed on the secret list. An independent investigation of the constitution of R.63 has been described recently by Mosher (*J. Amer. Chem. Soc.*, 1946, **68**, 1565). We had, however, followed a somewhat different approach to the problem and overlap in results is restricted to the following points:

Mosher is in agreement that R.63 (as prepared by Robinson and his co-workers) contains considerable 8- γ -aminopropylamino-6-methoxyquinoline (I) dihydrochloride (R.36) and some 4% of 8- γ -phthalimidopropylamino-6-methoxyquinoline (II), although he does not explain how the latter compound was formed. He has demonstrated the presence of a larger proportion (> 20%) of 8- γ' -aminopropyl- γ -aminopropylamino-6-methoxyquinoline trihydrochloride (R.120) than that reported here. Lastly, Mosher foreshadows our elucidation of the nature of the intermediate which separates in the hydrazine hydrolysis of *N*-substituted phthalimides.

A brief summary of the present paper appeared in *Nature* (1946, **158**, 514). Spring and Woods have since added further evidence for scheme (A) (*ibid.*, p. 754).

EXPERIMENTAL.

(Melting points are corrected.)

8- γ -Phthalimidopropylamino-6-methoxyquinoline (II).—8-Amino-6-methoxyquinoline (696 g.) (Barber and Wragg, *J.*, 1946, 612) was refluxed with 0.5 molar proportion of phthalo- γ -bromopropylimide (536 g.) in chlorobenzene (2 l.) for 12 hours. After a short delay, 8-amino-6-methoxyquinoline hydrobromide commenced to separate. This salt (404 g.; 76%) was collected from the cold reaction mixture and the filtrate diluted with alcohol (6 l.); 8- γ -phthalimidopropylamino-6-methoxyquinoline then separated as yellow felted needles. The product was collected after 24 hours, washed with light petroleum (2 l.)-alcohol (750 c.c.), and dried at 40°/11 mm., giving 403 g. (56%), m. p. 99–101°. The chlorobenzene-alcohol liquors were treated with excess of concentrated hydrochloric acid, and the precipitated orange hydrochloride was removed and washed with alcohol (500 c.c.). The damp salt (344 g.) was suspended in boiling alcohol (5 l.) and treated with a small excess of concentrated ammonia. 8- γ -Phthalimidopropylamino-6-methoxyquinoline (104 g.) crystallised, making a total yield of 70%. No 8-bis-(γ -phthalimidopropyl)amino-6-methoxyquinoline was obtained as a by-product under these conditions (cf. Glen and Robinson, *loc. cit.*; Mosher, *loc. cit.*).

8- γ -Aminopropylamino-6-methoxyquinoline (I).—(a) *Hydrolysis of (II) in cold chloroform-alcohol using 2.25 mols. of hydrazine hydrate.* 8- γ -Phthalimidopropylamino-6-methoxyquinoline (7.22 g.) dissolved in chloroform (50 c.c.) and alcohol (50 c.c.) was treated with hydrazine hydrate (4.5 c.c., 50% w/v aqueous solution). After 3 hours at room temperature a gelatinous white precipitate began to separate. After 4 days the solvents were removed at 40°/20 mm. and the residue shaken mechanically (2 hours) with a mixture of 2*N*-ammonia (30 c.c.), water (40 c.c.), and chloroform (70 c.c.). A small quantity of insoluble material (*ca.* 0.5 g.) was dissolved separately by warming with chloroform-ammonia solution and returned to the main bulk. The chloroform layer (A) was extracted with four portions of *N*-acetic acid (20 c.c.) which were bulked, basified with concentrated ammonia, and then exhaustively extracted with ether. This extract on distillation in a bulb tube (air-bath at 180°) at 0.01 mm. gave 8- γ -aminopropylamino-6-methoxyquinoline (4.1 g., 89%), n_D^{25} 1.637, converted into carbamate derivative, m. p. 113–116°. The chloroform (A) was evaporated to dryness, leaving a negligible dark red residue (0.2 g.). The aqueous ammoniacal layer, precipitated with concentrated hydrochloric acid, yielded 2.98 g. (92%) of phthalylhydrazide, m. p. 342–344°.

(b) *Hydrolysis of (II) in boiling alcohol with various proportions of hydrazine hydrate.* Hydrazine hydrate (40 c.c., 50% w/v aqueous solution; 0.8 mol.) was added to a solution of 8- γ -phthalimidopropylamino-6-methoxyquinoline (180 g.) in boiling alcohol (1.5 l.) and the mixture refluxed for 3 hours. The alcohol was removed under reduced pressure from the suspension of cream insoluble product, and the residue vigorously shaken with 2*N*-ammonia (500 c.c.), diluted with water (1 l.), and chloroform (2.5 l.). The aqueous alkaline layer was separated and acidified with concentrated hydrochloric acid; phthalylhydrazide separated (56 g.), m. p. 342–344°.

The chloroform layer was concentrated under reduced pressure to 700 c.c. and diluted with an equal volume of dry ether. Phthalobis- $[\gamma$ -(6-methoxy-8-quinolylamino)propyl]amide (V) separated (44 g.), m. p. 170–174°, crystallising from chloroform-methanol as tiny brown needles, m. p. 177–179° (Found: C, 68.7; H, 6.3; N, 14.0; OMe, 11.0; *M* (ebulliscope in chloroform), 600. $C_{24}H_{24}O_4N_4$ requires C, 68.9; H, 6.1; N, 14.2; OMe, 10.5%; *M*, 592). (V) was converted into the hydrochloride, m. p. 208–210° by treatment of a warm solution in chloroform-methanol with concentrated hydrochloric acid

(Found: N, 12.6; Cl, 10.6. $C_{13}H_{11}O_4N_3 \cdot 2HCl$ requires N, 12.6; Cl, 10.7%). This hydrochloride was readily reconverted into the base by suspension in a large volume of cold water.

The liquors from the separation of crude (V) above were evaporated to dryness under reduced pressure and the oily residue taken up in dry ether (1 l.). Carbon dioxide was passed, very slowly at first, into the filtered bright ethereal solution, precipitating the carbamate derived from (I) (63 g.) as a white powder, m. p. 112–114° [Found: C, 64.2; H, 7.0; N, 16.8. $(C_{13}H_{11}ON_3)_2CO_2$ requires C, 64.0; H, 6.76; N, 16.6%]. When a solution of the carbamate in warm methanol was treated with a small excess of concentrated hydrochloric acid the corresponding dihydrochloride, crystallising from methanol-ether in short orange needles, was obtained (96%). Drying over potash in a vacuum gave the anhydrous salt (cf. Beer, *loc. cit.*), m. p. 244–246° with slight previous shrinking from about 230° [Purification of many samples failed to give material, m. p. 251–252° (cf. Baldwin, *loc. cit.*; Beer, *loc. cit.*] (Found: N, 13.7; Cl, 23.5. Calc. for $C_{13}H_{11}ON_3 \cdot 2HCl$: N, 13.8; Cl, 23.4%). The free base (I) was prepared in 96% yield by dissolving the carbamate in a small excess of dilute hydrochloric acid at 80°, removing any dissolved carbon dioxide with a rapid stream of nitrogen for 10 minutes, basifying with concentrated aqueous ammonia, and extracting the liberated base with ether. Distillation of the residue on removal of the ether gave (I) as a single fraction, b. p. 160°/0.01 mm., a viscous yellow oil, n_D^{25} 1.637 (Found: C, 67.5; H, 7.4; N, 18.05. Calc. for $C_{13}H_{11}ON_3$: C, 67.5; H, 7.4; N, 18.2%), stored under an atmosphere of hydrogen. On long standing this sample solidified to a waxy solid, m. p. 37–38°.

In the experiment below where unchanged phthalimide (II) was recovered, this was isolated from the ethereal liquor after the precipitation and removal of the carbamate of (I).

The above experimental details exemplify the method of separation employed to obtain the results summarised in Table I.

TABLE I.

Reaction of the phthalimide (II) with hydrazine hydrate.

Reactants.			Products.			
	$+ N_2H_4 \cdot H_2O$	Time in boiling alcohol.			$+ R \cdot NH_2 +$	
(II)			unchanged (II)	(V)	(I), as carbamate.	(IV)
1.0 mol.	1.0 mol.	2 hrs.	none	0.075 mol.	0.57 mol.	Theoretical quantity
1.0 mol.	0.8 mol.	4 hrs.	none	0.15 mol.	0.5 mol.	"
1.0 mol.	0.5 mol.	10 hrs.	0.3 mol.	0.16 mol.	0.23 mol.	"

[R = γ -(6-methoxyquinolyl-8-amino)propyl.]

The products obtained, when the phthalimide (V) was treated with aqueous hydrochloric acid under various conditions, were separated and identified by means very similar to those described in the case of Table I. These results are summarised in Table II.

TABLE II.

Reaction of the phthalimide (V) with acid.

Reactants.		Conditions.	Products.		
	$+ \text{aqueous HCl}$			$+ \text{phthalimide (II)}$	$+ R \cdot NH_2$
(V)			unchanged. (V)	(II)	(I) as carbamate.
2 g.	90 c.c., 10%	1 hr. reflux	none	0.8 g.	trace
2 g.	30 c.c., 2N	30 mins. at 95°	none	1.05 g.	0.6 g.
2 g.	30 c.c., N	15 mins. at 95°	0.75 g.	0.57 g.	0.17 g.
2 g.	30 c.c., N	15 mins. at 70°	1.75 g.	none	trace

[R = γ -(6-methoxyquinolyl-8-amino)propyl.]

Model Experiments.—(a) *Exemplification of scheme (C) where R = benzyl.* Phthalobenzylimide (23.7 g.) was suspended in alcohol (200 c.c.), boiling under reflux, and hydrazine hydrate (10 c.c., 50% w/v aqueous solution; 1.0 mol.) added. After 2 hours the reaction mixture was cooled and the white crystalline product collected (21.3 g.). After being dried in the steam-oven for 1 hour this material analysed for the anhydrous phthalylhydrazide (IV) salt of benzylamine, m. p. 326–346° (Found: C, 66.8; H, 5.4; N, 15.5. $C_{18}H_{15}O_2N_3 \cdot C_7H_7N$ requires C, 67.0; H, 5.6; N, 15.6%). 2 G. of this salt were dissociated by one crystallisation from alcohol (200 c.c.); phthalylhydrazide alone separated, m. p. 342–346° (Found: C, 59.6; H, 4.0; N, 17.5. Calc. for $C_{18}H_{15}O_2N_3$: C, 59.3; H, 3.7; N, 17.3%). Dissociation was also effected by heating the salt (5.4 g.) at 120–140°/0.05 mm. for 3 hours. The

distillate, collected in a solid carbon dioxide-acetone cooled receiver, was anhydrous benzylamine (1.66 g.; 78%). (Found: *M*, by titration, 107. Calc. for C_7H_9N : *M*, 107).

(b) *Exemplification of scheme (D)*. Phthalo-*n*-propylimide (10 g.) and benzylamine (11.4 g.; 2 mol.) were fused in a distillation flask fitted with a Vigreux column. The melt was slowly heated to 180°. The distillate (b. p. 49°), collected in a cooled receiver, was anhydrous propylamine (1.8 g., 59%) contaminated by a small proportion of benzylamine. The residue, crystallised twice from chloroform, was phthalo-*NN'*-dibenzylamide, m. p. 176—178° (Tingle and Lovelace, *Amer. Chem. J.*, 1907, **38**, 651, give m. p. 178—179°).

(c) *Exemplification of scheme (E)*. 8- γ -Aminopropylamino-6-methoxyquinoline (2.2 g.) was fused with phthalo-*n*-propylimide (1.89 g.) for 8 hours at 110—115°. The *n*-propylamine (44%) evolved from the melt was removed in a slow stream of hydrogen which was subsequently scrubbed with standard acid. The fusion product was dissolved in methanol (40 c.c.). On cooling, the phthalamide (V) separated, 1.06 g., m. p. 157—171°. Recrystallisation from chloroform-methanol gave 0.9 g., m. p. 176—178°; mixed m. p. with authentic material was 175—178°. On standing, the liquors from the crude phthalamide (V) precipitated the phthalimide (II) (0.64 g.) (*A*), m. p. 97—99°, characterised by mixed m. p. 100—101° with authentic material after recrystallisation from methanol. The methanol liquors from (*A*) were concentrated, and the residue dissolved in ether was treated with carbon dioxide, precipitating the carbamate of the amine (I) (0.5 g.), m. p. 112—116°.

(d) *Exemplification of scheme (F)*. An equimolar mixture of the phthalamide (V) (5.9 g.) and phthalo-*n*-propylimide (1.9 g.) were fused at 165° for 1 hour, during which time *n*-propylamine was evolved. The fusion product was dissolved in alcohol (50 c.c.) from which 3.5 g. (48%) of bulky yellow needles separated, m. p. 84—100°. Recrystallisation from alcohol gave the phthalimide (II) (3.2 g.), m. p. 99—101°, characterised by mixed m. p. with an authentic sample.

(e) *Exemplification of scheme (G)*. The phthalamide (V) (1.18 g.) was refluxed for 10 hours in chlorobenzene (20 c.c.) with phthalo- γ -bromopropylimide (1.07 g.). The hydrochloride precipitated from the mixture by alcoholic hydrogen chloride was crystallised twice from alcohol and then converted in aqueous methanol into the base, long bulky yellow needles from methanol (0.2 g.), m. p. 99—101°, shown to be the phthalimide (II) by mixed m. p.

(f) *Exemplification of scheme (H)*. (i) Equimolar proportions of the amine (I) (2.31 g.) and the phthalimide (II) (3.61 g.) were refluxed for 1 hour in alcohol (70 c.c.). The total product which separated on cooling was crystallised from chloroform-ether; the phthalamide (V) (2.05 g.) was thus obtained, m. p. 173—176° (identity confirmed by mixed m. p.).

(ii) A theoretical yield of the phthalamide (V) was obtained when the above reaction was carried out by fusion for 1 hour at 115°.

(iii) A 70% yield of the phthalamide (V) was similarly obtained from the fusion of the amine (I) (5.1 g.; 2 mols.) and phthalic anhydride (1.5 g.) at 115° for 1 hour.

(iv) A theoretical yield of phthalo-*NN'*-dibenzylamide was similarly obtained by fusion of equimolecular quantities of phthalobenzylimide and benzylamine at 120° for 1½ hours.

First Stage of the Preparation of R.63. Separation of the Reaction Products of the Fusion of 8- γ -Aminopropylamino-6-methoxyquinoline (I) with Phthalo- γ -bromopropylimide (VI).—The identification of unchanged (I) and the phthalimide (II) as products of this reaction has been confirmed at least twice, both after 15 minute and 7 hour fusions. The following are typical experiments:

(a) *Method of fusion*. Equimolar proportions of (I) (6 g.) and (VI) (7 g.) were mixed by rotation of the reaction flask, closed by a calcium chloride tube, and immersed in an oil-bath at 115°. The mixture fused to a mobile liquid which rapidly thickened to a red-brown glass.

(b) *Isolation of 8- γ -phthalimidopropylamino-6-methoxyquinoline (II)*. The glassy product from a 7 hour fusion as in (a) was dissolved in glacial acetic acid (15 c.c.) with mechanical shaking (10 hours). The orange-brown precipitate which separated was filtered from the viscous red liquor, washed with three portions of glacial acetic acid (5 c.c.) and then ether, giving 1.7 g., m. p. 190—200°. This was repeatedly recrystallised from methanol until the orange hydrobromide obtained (0.98 g.), m. p. 214—220°, was sufficiently pure to yield 0.3 g. of phthalimide (II), m. p. 102—103° (identity confirmed by mixed m. p.), on treatment with ammoniacal methanol. By dilution with water and recrystallisation of the precipitate, a further 0.1 g., m. p. 100—103°, of the phthalimide (II) was isolated from the mother liquor. The original acetic acid liquors were stored at 0° (2 days) when a further 0.6 g. of orange material separated. This crystallised from methanol giving 0.35 g., m. p. 220—225°, which on conversion into the base (0.09 g.) was characterised by mixed m. p. 101—103° as the phthalimide (II).

(c) *Isolation of 8- γ -aminopropylamino-6-methoxyquinoline (I)*. The fusion product from a 7 hour reaction as (a) was dissolved with mechanical shaking in chloroform (50 c.c.). The solution was shaken with 2*N*-ammonia (12 c.c.) and water (20 c.c.). The chloroform layer was then extracted with four 2 c.c. portions of 2*N*-acetic acid in water (20 c.c.) until the last extract was acid (litmus). The combined extracts were counter-extracted (chloroform) and then basified slowly with 2*N*-ammonia in the presence of ether (500 c.c.). The aqueous layer was then made strongly alkaline with concentrated ammonia and saturated with salt. The dried (K_2CO_3) ether layer was evaporated and distilled in a bulb tube (air-bath up to 200°) at 0.01 mm. About half the residue distilled, yielding a light brown oil, 2.0 g., n_D^{20} 1.631. This was taken up in ether and converted into the carbamate of (I) (0.7 g., 10% recovery), m. p. 100—108°, decomposing in a bulb tube to give pure (I) (0.5 g.), n_D^{20} 1.636, reconverted into carbamate derivative, m. p. 109—115° (mixed melting point with authentic material 113—116°).

(d) *Isolation of 8- γ' -phthalimidopropyl- γ -aminopropylamino-6-methoxyquinoline (VII)*. The product from a 7 hour fusion, as (a) was dissolved in pyridine (25 c.c.). The brown oil precipitated with water (300 c.c.) was twice extracted by boiling with a supernatant layer of ether (100 c.c.). The residue separated by decantation was dissolved in methanol (100 c.c.) and diluted with an equal volume of ether. The precipitated gum solidified on standing. The solid was collected and recrystallised from methanol, forming long rectangular light brown plates, m. p. 174—177°, which proved to be 8- γ' -phthalimidopropyl- γ -aminopropylamino-6-methoxyquinoline monohydrobromide (Found: C, 57.4; H, 5.1; N, 11.0; Br, 16.8. $C_{24}H_{28}O_3N_4.HBr$ requires C, 57.7; H, 5.4; N, 11.2; Br, 16.1%). We con-

cluded that this product was not 8- γ -aminopropylamino-6-methoxy-1- γ -phthalimidopropylquinolinium bromide, or 8- γ -aminopropyl- γ -phthalimidopropylamino-6-methoxyquinoline hydrobromide, compounds of the same empirical formula, because no primary amine group could be detected in a micro-Van Slyke determination, for which we are indebted to Miss P. Garwood of Imperial College, S.W. 7.

(e) *Typical analytical experiment in outline.* The product from a 15 minute fusion, as in (a), was dissolved in alcohol (50 c.c.). The solution was slowly added to well-stirred ether (300 c.c.). The milky product was shaken with 100 c.c. water and then extracted with *n*-hydrochloric acid (20 c.c.). The bright ether layer was dried (K_2CO_3) and evaporated to give 1.3 g. (18% recovery) of unchanged phthalo- γ -bromopropylimide (VI), m. p. 69–72°. The bulked aqueous extracts were basified with 50% sodium hydroxide and the total bases taken up into chloroform (150 c.c.) (A). This was extracted with 2*N*-acetic acid (25 c.c.) in water (50 c.c.), and the extracted material taken as base into ether. This dried (K_2CO_3) ether extract yielded the carbamate of (I) (1.0 g., 16% recovery). The chloroform (A) was next removed and the residue converted into hydrochloride (B) which was crystallised from alcohol. The insoluble hydrochloride of the phthalimide (II) (1.6 g., 15%) was first obtained. This was repeatedly crystallised from methanol, and, when sufficiently pure, converted into base confirmed to be (II) by m. p. and mixed m. p. The more soluble hydrochloride in the mixture (B) was crystallised from alcohol-ether many times without a pure substance being definitely characterised, although a N : Cl ratio of 2.07/1 indicated 8- γ' -phthalimidopropyl- γ -aminopropylamino-6-methoxyquinoline (VII) dihydrochloride.

The above results are summarised in Table III, together with Van Slyke estimations for primary amino-group on the products of fusions [as (a)] of varying duration.

TABLE III.

R.63 fusion. Progress of reaction.

Duration of fusion.....	Nil.	5 mins.	15 mins.	7 hrs.
Van Slyke estimation of N present as primary amino-group (%)	6.4, 6.3*	2.1	—	2.4
Proportion of amine (I) recovered unchanged (%)	—	—	16	10
Proportion of phthalimide (VI) recovered unchanged (%)	—	—	18	—
Proportion of theoretically possible phthalimide (II) actually isolated as crude hydrobromide (%)	—	—	15	22†

* Amine (I) requires 6.06%.

† 5% as pure base.

Preparation of R.63 for Antimalarial Test.—The procedure of Glen and Robinson (*loc. cit.*) was exactly followed [Found on our sample of R.63 : N as primary amino-group (Van Slyke), 4.85. Calc. for amine (I) dihydrochloride, 4.6. Calc. for 8- γ' -aminopropyl- γ -aminopropylamino-6-methoxyquinoline trihydrochloride, 3.5%].

8-*Bis-(γ -phthalimidopropyl)amino-6-methoxyquinoline.*—8- γ -Phthalimidopropylamino-6-methoxyquinoline (20 g.) was fused with exclusion of moisture with phthalo- γ -bromopropylimide (32 g.) for 12 hours at 120°. The red glassy product was dissolved in methanol (200 c.c.), and an orange hydrobromide (20 g.) crystallised out. This was converted into base in methanol-2*N*-ammonia. 8-*Bis-(γ -phthalimidopropyl)amino-6-methoxyquinoline* crystallised from pyridine-methanol, m. p. 165–167° (13 g., 43%) (cf. Quin and Robinson, *loc. cit.*).

8- γ -*Phthalamidopropylamino-6-methoxyquinoline.*—8- γ -Phthalimidopropylamino-6-methoxyquinoline (20 g.) was added to a boiling solution of potassium hydroxide (13.8 g.) in alcohol (275 c.c.). After 30 minutes the mixture was cooled to 0° and almost neutralised with 2*N*-hydrochloric acid. The precipitated salt was just dissolved by adding water (200 c.c.) and the alcohol removed at 30 mm. The remaining liquor (charcoaled) was just acidified (litmus) cold with glacial acetic acid. The precipitated *product* was crystallised from aqueous methanol and dried over phosphoric oxide at 10 mm. (Found : C, 63.7; H, 6.1; N, 10.7; *M*, by titration, 390. $C_{21}H_{21}O_4N_3 \cdot H_2O$ requires C, 63.5; H, 5.8; N, 10.6%; *M*, 397). The loss in weight at 100° on this hydrated acid (Found : 9.2. $C_{21}H_{21}O_4N_3 \cdot H_2O$ requires 4.54%) indicated that both dehydration and ring closure had occurred, giving the phthalimide (II). This was confirmed by m. p. 101–103° and mixed m. p. 101–104° with authentic material after one crystallisation from methanol.

We are indebted to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, and to the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES,
MAY & BAKER LTD., DAGENHAM, ESSEX.

[Received, December 6th, 1946.]

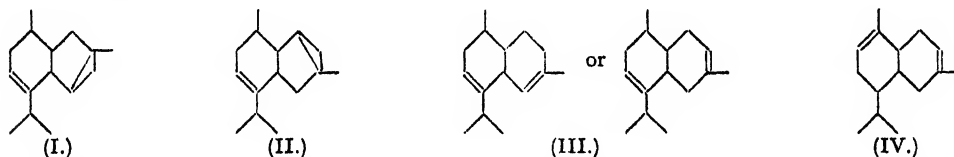
245. The Constitution of Copæne.

By LINDSAY H. BRIGGS and WILLIAM I. TAYLOR.

The constitution of copæne has been elucidated on the basis of the following sequence of reactions. Perbenzoic acid yields the oxide, converted by methylmagnesium iodide into the corresponding methylcarbinol which after dehydration and dehydrogenation furnishes the known compound, 1 : 6 : 7-trimethyl-4-isopropynaphthalene.

THE tricyclic sesquiterpene copæne is a comparatively rare constituent of essential oils, and so far it has only been detected in the oils of *Oxystigma mannii* (Schimmel's Report, 1914, April, p. 48), *Sindora wallichii* (Henderson, McNab, and Robertson, J., 1926, 3077), *S. inermis* (Huzita, J. Chem. Soc. Japan, 1941, 62, 431), *Dysoxylum fraserianum* (Penfold, J. Proc. Roy. Soc. New South Wales, 1928, 61, 337) and *Cedrela toona* (Pillai and Rao, J. Soc. Chem. Ind., 1931, 50, 220r). More recently it has been identified by Briggs and Sutherland (forthcoming publication) in the oil of the New Zealand tree, *Phyllocladus trichomanoides*, the source for the present investigation.

From the molecular refraction, the formation of a dihydro-derivative, and the oxidation by ozone or potassium permanganate to a monobasic ketonic acid, copæne ketonic acid, $C_{15}H_{24}O_2$, copæne was shown by Semmler and Stenzel (*Ber.*, 1914, 47, 2555) to be tricyclic with one ethylene linkage. Since it also gave *l*-cadinene dihydrochloride with hydrogen chloride it must contain the cadinene skeleton and a cyclopropane ring, later confirmed by Henderson *et al.* (*loc. cit.*) by dehydrogenation with sulphur to cadalene. By further oxidation of copæne ketonic acid with sodium hypobromite, Semmler and Stenzel obtained a dibasic acid, copæne-dicarboxylic acid, $C_{12}H_{18}O_4$ (*vide infra*), apparently by the elimination of an isopropyl group. The provisional formula (I) suggested by Semmler and Stenzel was changed to (II) by Henderson *et al.* in view of the structure (III) proposed by Ruzicka and Stoll (*Helv. Chim. Acta*, 1924, 7, 84) for cadinene.



In view of the revised structure for cadinene (IV) put forward on a firm experimental basis by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, 64, 417) that of copæne also required revision.

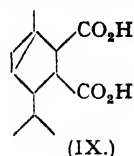
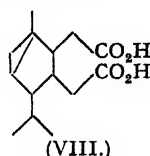
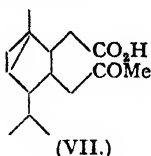
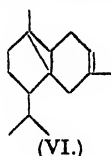
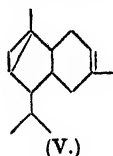
The position of the double bond at C_6-C_7 in copæne has now been established by the method used by Ruzicka and Sternbach (*Helv. Chim. Acta*, 1940, 23, 124) for determining the position of the double bond in *d*-pimaric acid and applied by Campbell and Soffer (*loc. cit.*) and Soffer, Steinhardt, Turner, and Stebbins (*J. Amer. Chem. Soc.*, 1944, 66, 1520) for the constitution of cadinene and isozingiberene respectively.

Copæne was converted quantitatively into the oxide by the action of perbenzoic acid. On distillation in high vacuum, however, three fractions were obtained, indicating that some isomerisation to the ketone or fission of the cyclopropane ring had occurred. Since the isomeric ketone should give the same product ultimately as the oxide, the combined distillate was treated with excess of methylmagnesium iodide and the resultant methylcarbinol dehydrated with formic acid. Dehydrogenation with palladised charcoal failed to yield an aromatic hydrocarbon, but this was formed with selenium. The dehydrogenation products, after being washed with alkali, were distilled, small fractions being taken off empirically and converted into picrates. From two fractions the picrate of 1 : 6 : 7-trimethyl-4-isopropynaphthalene was obtained after repeated crystallisation, the purest specimen having m. p. 121–122°. Campbell and Soffer (*loc. cit.*) record m. p. 122–123° for their synthetic material. The double bond in copæne must therefore be in the 6–7 position.

From the alkaline washings of the dehydrogenation product a crystalline naphthol, $C_{15}H_{18}O$, was obtained (picrate, trinitrobenzoate) which is probably the previously unknown 7-hydroxy-1 : 6-dimethyl-4-isopropynaphthalene arising from the dehydrogenation of unmethylated copæne oxide or the isomeric ketone. We hope to report later on this compound.

Since copæne forms *l*-cadinene dihydrochloride with hydrogen chloride, the three-membered ring must have one point of attachment at C_1 and the other at C_2 (V) or C_{10} (VI). If the latter, then dehydrogenation should yield an azulene as well as cadalene as in the case of ledene

(Komppa and Nyman, *Compt. rend. Trav. Lab. Carlsberg*, 1938, 22, 272) or azulene alone as in aromadendrene (Radcliffe and Short, *J.*, 1938, 1200). Since no trace of azulene is obtained from copæne the three membered ring must be at C₁-C₃ and copæne must be formulated as (V).



The copæne ketonic acid, C₁₅H₂₄O₃, of Semmler and Stenzel must now be revised to (VII), and the dibasic acid, copænedicarboxylic acid, obtained on sodium hypobromite oxidation, is more probably the normal product (VIII), C₁₄H₂₂O₄, rather than (IX) C₁₂H₁₈O₄, with which, however, the analytical figures agree.

EXPERIMENTAL.

The copæne used in these experiments was repeatedly fractionated, finally through a 20 plate column, and then had the following constants: b. p. 114–114.5°/10 mm.; d_4^{20} 0.9055 (constant); n_D^{20} 1.4880–1.4895; $[\alpha]_D^{25}$ –0.44° to +1.20°; it had been identified by Briggs and Sutherland (*loc. cit.*) by the formation of *l*-cadinene dihydrochloride with hydrogen chloride, dehydrogenation to cadalene with palladised charcoal, and oxidation to copæne ketonic acid, characterised as the semicarbazone, m. p. 222°, and the semicarbazone of its methyl ester, m. p. 194–196°.

Copæne Oxide.—A solution of copæne (11.1 g.) in chloroform (200 c.c.) was added to a twofold excess of perbenzoic acid in chloroform (300 c.c.) at 6° and left overnight. Titration of an aliquot portion against standard thiosulphate solution after addition of potassium iodide then showed that reaction was complete. The chloroform solution, after being washed with sodium carbonate and sodium thiosulphate solutions, yielded a viscous colourless oil (11.9 g.), separated by distillation into the following fractions: (1) b. p. 112–120°/0.5 mm., 4.09 g.; (2) b. p. 95–105°/0.03 mm., 2.24 g.; (3) b. p. 127–130°/0.05 mm., 1.37 g.

Methylation and Dehydration.—The combined fractions (7.3 g.) in dry ether (30 c.c.) were slowly added to an ethereal solution of methylmagnesium iodide (3 molal excess), and after the first action had ceased the mixture was refluxed for 30 hours. After decomposition with saturated ammonium chloride solution the reaction mixture was extracted with ether, and the extract, after being washed with brine containing sodium carbonate, then with water, and dried (Na₂SO₄), yielded on distillation of the ether a syrupy product (6.43 g.) in 82% yield. This was boiled under reflux with formic acid (15 c.c.) for 15 minutes and, after addition of water, the product was isolated through light petroleum; yield 5.97 g.

Dehydrogenation.—The dehydrated oil (1.43 g.) and selenium (2.08 g.) were heated slowly to 200° until water ceased to be evolved, the temperature was then maintained at 220° for 16 hours and at 300° for a further 9 hours. The product was extracted with light petroleum, and the solution washed with sodium hydroxide solution and water, and dried; after removal of the solvent 0.864 g. of a slightly fluorescent oil was obtained. On distillation at 10 mm. (bath temperature 120°) five fractions were obtained weighing successively 0.2286 g., 0.0987 g., 0.0736 g., 0.1466 g., and 0.0411 g., leaving 0.2090 g. of a residual black tar. The first three fractions failed to yield a pure picrate. From the fourth fraction a crude red picrate (200 mg.) was obtained, m. p. 95°, which after six crystallisations from methyl alcohol furnished 8 mg. of long needles of constant m. p. 121–122° (Found: C, 60.10; H, 5.47; N, 9.35. Calc. for C₁₅H₂₀, C₈H₃O₂N₃: C, 59.85; H, 5.25; N, 9.52%). From the mother liquors of the fourth fraction a small amount of impure cadalene picrate, m. p. 110–111°, was isolated which on being mixed with an authentic specimen softened at 100° and melted at 109–112°. The fifth fraction yielded the impure picrate of 1:6:7-trimethyl-4-isopropyl-naphthalene, m. p. 117–118°, undepressed by a pure specimen obtained from the fourth fraction.

From the alkaline washings of the dehydrogenation product a crude *naphthol* was obtained on acidification and purified by sublimation at 100°/0.01 mm.; yield 30 mg. The product recrystallised from methyl alcohol as woolly needles, m. p. 116° (Found: C, 83.54, 83.58; H, 8.50, 8.66. C₁₅H₁₈O requires C, 84.05; H, 8.46%). The dark red picrate separated from methyl alcohol in short needles, m. p. 139°, and the bright red trinitrobenzoate similarly in long needles, m. p. 139–140°.

The analyses are by Drs. Weiler and Strauss, Oxford.

We are indebted to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants, and to Dr. L. M. Cooke for Monel metal gauze used in the fractionating column. One of us (W. I. T.) is indebted for a Duffus Lubecki Scholarship.

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[Received, December 9th, 1946.]

246. Some Derivatives of D-Galacturonic Acid.

By J. K. N. JONES and M. STACEY.

The synthesis is described of some derivatives of D-galacturonic acid, in particular 2-methyl α -methyl-D-galacturonoside methyl ester. This compound was oxidised to 2-methyl galactosaccharic acid (2-methyl mucic acid) a useful reference compound, while under stronger oxidising conditions some demethylation occurred with formation of galactosaccharic acid (mucic acid).

In addition to its widespread occurrence in plant gums and pectins, D-galacturonic acid forms a constituent of certain bacterial polysaccharides, e.g., the Type I *pneumococcus* specific polysaccharide (Heidelberger, Goebel, and Avery, *J. Exp. Med.*, 1925, 42, 701), and the polysaccharide of *Coccidioides immitis* (Hassid, Baker, and McCready, *J. Biol. Chem.*, 1943, 149, 303).

It was necessary to synthesise partly methylated derivatives of D-galacturonic acid to serve as reference compounds in determination of bacterial polysaccharide structure. D-Galacturonic acid, obtained both by synthesis from D-galactose (Stacey, *J.*, 1939, 1529) and from citrus pectin by enzymic degradation, was converted into α -methyl-D-galacturonoside methyl ester [which has the pyranose structure (Levene and Kreider, *J. Biol. Chem.*, 1937, 120, 597)] by boiling it with 1% methanolic hydrogen chloride for 8 hours. Treatment of this ester for 15 hours with acetone containing either 0.4% hydrochloric acid or anhydrous copper sulphate with a trace of concentrated sulphuric acid converted it into 3:4-monoacetone α -methyl-D-galacturonoside methyl ester (m. p. 107°; monohydrate, m. p. 70°).

This product was transformed on methylation with silver oxide and methyl iodide into the syrupy 2-methyl derivative. On being kept in a moist atmosphere the syrup crystallised in the form of its monohydrate. Removal of the acetone groups gave syrupy 2-methyl α -methyl-D-galacturonoside methyl ester (amide, m. p. 174°) which on being oxidised with nitric acid under moderate conditions gave 2-methyl galactosaccharic acid, a liquid (amide, m. p. 200°). Under more drastic oxidation conditions with nitric acid there was observed an unusual case of demethylation with production of free galactosaccharic acid in fairly good yield; cf. Anderson and Otis (*J. Amer. Chem. Soc.*, 1930, 52, 4462), who effected the removal of non-glycosidic methyl residues from a mesquite gum by means of 72% sulphuric acid.

EXPERIMENTAL.

D-Galacturonic Acid.—This was prepared both from citrus pectin by the action of the enzyme, "Pectinol IOM," and from D-galactose by the synthetic method of Stacey (*loc. cit.*).

α -Methyl-D-galacturonoside Methyl Ester.—D-Galacturonic acid (5 g.) was boiled for 8 hours with 1% methanolic hydrogen chloride. The solution, neutralised with lead carbonate, was filtered and evaporated under diminished pressure to a syrup which rapidly crystallised. When recrystallised from methyl alcohol-acetone the substance had m. p. 147°, yield 50%, $[\alpha]_D^{20} +128^\circ$ (c, 1.0 in water); cf. Morell and Link (*J. Biol. Chem.*, 1933, 100, 385).

3:4-Monoacetone α -Methyl-D-galacturonoside Methyl Ester.—(a) α -Methyl-D-galacturonoside methyl ester (1.2 g.) was shaken with acetone (50 c.c.) containing hydrogen chloride (0.2 g.) for 15 hours. The clear solution was poured into aqueous sodium hydrogen carbonate and the 3:4-monoacetone derivative extracted with chloroform. The extracts were dried ($MgSO_4$), and the filtered solution was evaporated in a vacuum. The compound (1.1 g.) had m. p. 107° (Found: C, 50.1; H, 6.8; OMe, 23.4. $C_{11}H_{18}O_7$ requires C, 50.4; H, 6.9; OMe, 23.6%).

(b) α -Methyl-D-galacturonoside methyl ester (5 g.) was shaken for 12 hours in acetone (200 c.c.) containing anhydrous copper sulphate (5 g.) and concentrated sulphuric acid (0.5 g.). The acid was neutralised with copper carbonate, and the filtered solution on evaporation yielded a crystalline product. When recrystallised from acetone-ligroin the product (4.5 g.) formed large prisms, m. p. 74°. On being heated or on being kept in a vacuum desiccator the crystals lost one molecule of water giving a product in the form of a fine white powder, m. p. 107°, $[\alpha]_D^{20} +118^\circ$ (c, 1.0 in water) (Found: C, 50.0; H, 6.9; OMe, 23.6%).

3:4-Monoacetone 2-Methyl α -Methyl-D-galacturonoside Methyl Ester.—The above monoacetone compound (3.0 g.) was dried and methylated thrice with silver oxide and methyl iodide, giving the ester as a syrup (3.0 g.), b. p. 124° (bath temp.)/0.3 mm., n_D^{20} 1.4210 (Found: OMe, 33.5. $C_{12}H_{20}O_7$ requires OMe, 33.7%). On exposure to a moist atmosphere the syrup slowly crystallised. When recrystallised from ethyl alcohol-ligroin the monohydrate had m. p. 38°, $[\alpha]_D^{20} +116^\circ$ (c, 1.1 in water) (Found: C, 49.2; H, 7.5; OMe, 32.4. $C_{12}H_{20}O_7 \cdot H_2O$ requires C, 49.1; H, 7.6; OMe, 31.8%).

2-Methyl α -Methyl-D-galacturonoside Methyl Ester.—A sample of the above compound (0.33 g.) was hydrolysed with boiling 33% acetic acid which converted it into a syrupy mixture of 2-methyl α -methyl-D-galacturonic acid and its methyl ester (Found: OMe, 35.7. Calc. for $C_9H_{14}O_7$: OMe, 27.7. Calc. for $C_9H_{14}O_7$: OMe, 39.5%). The syrup was dissolved in methyl alcohol and esterified by the addition of excess of diazomethane. After 2 hours the solvent was removed under reduced pressure and the residual syrup distilled; b. p. 190° (bath temp.)/0.3 mm., n_D^{21} 1.4732, $[\alpha]_D^{20} +80^\circ$ (c, 1.1 in water) (Found: OMe, 37.5. $C_9H_{14}O_7$ requires OMe, 39.5%). The ester was converted in the usual way into the amide which slowly crystallised; m. p. 174°, $[\alpha]_D^{20} +55^\circ$ (c, 0.05 in alcohol) (after recrystallisation from absolute ethanol-ether) (Found: N, 6.3; OMe, 27.5. $C_9H_{14}O_6N$ requires N, 6.3; OMe, 28.1%).

Oxidation of 2-Methyl 3 : 4-Monoacetone α -Methyl-D-galacturonoside Methyl Ester.—(a) A sample of the syrupy monoacetone compound (1.3 g.) was oxidised by treating it at 100° for 35 minutes with nitric acid (*d* 1.3). There was a copious deposit of crystalline material (0.5 g.) which was difficult to recrystallise. It had m. p. 219° (decomp.) alone or in admixture with galactosaccharic acid.

From the mother liquor there was obtained a small amount of oxalic acid and a syrup (0.5 g.) which was a mixture of ill-defined products.

(b) A further carefully redistilled fraction of the monoacetone compound (0.6 g.) was hydrolysed and the products were oxidised by heating them at 80° for 15 minutes with nitric acid (*d* 1.3). On being kept overnight the solution deposited only a trace of galactosaccharic acid. The nitric acid was distilled off with water and the syrupy product converted to the methyl ester (0.8 g.) which was distilled in a high vacuum; b. p. 160–162° (bath temp.)/0.07 mm., $[\alpha]_D^{20} -19^\circ$ (*c*, 0.27 in water), yield 0.5 g. The ester was converted into an *amide* which crystallised from water in the form of long needles, m. p. 200°, and gave a positive Weerman reaction (Found: C, 38.0; H, 6.5; N, 12.3; OMe, 14.4. $C_7H_{14}O_6N_2$ requires C, 37.8; H, 6.3; N, 12.6; OMe, 14.2%).

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[Received, December 12th, 1946.]

247. *Synthesis of Some Derivatives of D- and L-Arabinose.*

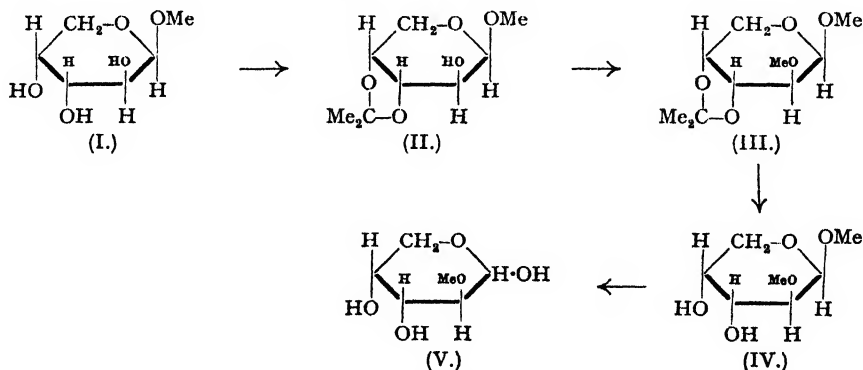
By J. K. N. JONES, P. W. KENT, and M. STACEY.

D-Arabinose has been converted into 2-methyl D-arabinose via 3 : 4-monoacetone β -methyl-D-arabopyranoside and its 2-methyl derivative. Crystalline 2-p-toluenesulphonyl 3 : 4-monoacetone β -methyl-D-arabopyranoside has also been isolated together with the crystalline p-toluenesulphonylhydrazide of 2-methyl D-arabinose. Analogous compounds, as well as the crystalline anilide of 2-methyl monoacetone L-arabinose, have been obtained from L-arabinose.

THE identification of D-arabofuranose as a constituent sugar of the polysaccharides of *M. tuberculosis* (Haworth, Stacey, and Kent, *Abs. Amer. Chem. Soc.*, Chicago Meeting, 1946, 5 R.) is of considerable interest. Although the L-isomer has been found extensively in natural polysaccharides such as the plant gums, reports of the occurrence of D-arabinose in natural compounds are comparatively rare. Its presence in barbaloin has been claimed by Leger (*Bull. Soc. chim.*, 1910, 7, 800) and it has been found in some animal secretions (Neuberg and Wohlge-muth, *Z. physiol. Chem.*, 1902, 35, 31).

The wide occurrence of L-arabinose has led to the formation and study of many of its derivatives whereas the reactions and compounds of D-arabinose are incompletely known. With a view to obtaining reference compounds and to the chemical synthesis of biologically important pentose-related substances, *e.g.*, 2-deoxyribose compounds, a number of derivatives of D-arabinose were synthesised. The present paper describes these and also some derivatives of L-arabinose required for similar purposes.

D-Arabinose obtained from calcium gluconate by essentially the method of Hockett and Hudson (*J. Amer. Chem. Soc.*, 1934, 56, 1562) was converted into crystalline β -methyl-D-arabopyranoside (I). When this compound was treated with acetone in the presence of a suitable dehydrating agent, it gave a syrupy monoacetone derivative which was shown to be 3 : 4-monoacetone β -methyl-D-arabopyranoside (II) as follows. On its being methylated with



methyl iodide and silver oxide there was formed a crystalline monomethyl monoacetone β -methyl-D-arabopyranoside (III) (m. p. 45°) which, on hydrolysis with methanolic hydrogen

chloride, afforded the 2-methyl β -methyl-D-arabopyranoside (IV) of von Schmidt and Simon (*J. pr. Chem.*, 1939, 152, 190). This compound underwent further hydrolysis with aqueous acid giving 2-methyl D-arabinose (V) which was converted into a crystalline *p*-toluenesulphonyl-hydrazone having properties identical with those of the β -methyl-D-arabinose *p*-toluenesulphonylhydrazone obtained by von Schmidt and Simon (*loc. cit.*) by the degradation of 3-methyl D-glucose.

From the monoacetone glycoside (II) there were obtained the crystalline 2-*p*-toluenesulphonyl and 2-methanesulphonyl derivatives (m. p. 134° and 135° respectively), which could not be converted directly into the 2-iodo-compound.

In the presence of acetone and excess of concentrated sulphuric acid, β -methyl-D-arabopyranoside and monoacetone β -methyl-D-arabopyranoside, lost their glycosidic groups and were converted into diacetone D-arabinose which had properties analogous to those of the diacetone L-arabinose synthesised by Svanberg and Bergman (*Chem. Zentr.*, 1924, i, 1021).

It has been reported (Ohle and Berend, *Ber.*, 1927, 60, 810) that treatment of L-arabinose with acetone in the presence of anhydrous cupric sulphate gave a monoacetone derivative which reduced Fehling's solution. An analogous *monoacetone* derivative has now been prepared from D-arabinose, and although the structure of this has not been fully investigated it is likely that the *isopropylidene* group engages the 3:4-positions. Thus on further treatment with acetone containing 2% sulphuric acid the monoacetone compound was converted into a non-reducing diacetone D-arabinose. This was identical with a diacetone D-arabinose prepared by the action of acetone containing 3% sulphuric acid upon either β -methyl-D-arabinoside or monoacetone β -methyl-D-arabopyranoside in which it is known that the acetone group engaged the 3:4-positions.

In the L-series, β -methyl-L-arabopyranoside was converted into 3:4-monoacetone β -methyl-L-arabopyranoside, from which a crystalline 2-toluenesulphonyl derivative (m. p. 134°) was obtained. Methylation of the monoacetone glycoside afforded 2-methyl 3:4-monoacetone β -methyl-L-arabopyranoside. In this compound scission of the acetone group was effected by treatment with acetic acid, and the product, 2-methyl β -methyl-L-arabopyranoside, was hydrolysed with dilute sulphuric acid giving 2-methyl L-arabinose from which a crystalline *phenylhydrazone* was isolated.

Treatment of 2-methyl L-arabinose with acetone in the presence of a dehydrating agent yielded a crystalline 2-methyl *monoacetone* L-arabinose which was reducing to Fehling's solution and, on being boiled with ethanolic aniline, gave a readily crystallised *anilide*.

EXPERIMENTAL.

D-Arabinose from Calcium D-Gluconate.—The method employed was a modification of that described by Hockett and Hudson (*J. Amer. Chem. Soc.*, 1934, 56, 1632). A solution of ferric acetate, prepared by addition of 21 g. of ferric sulphate in 60 c.c. of water to 10.5 g. of barium acetate in 60 c.c. of water, was mixed with calcium D-gluconate (200 g. in 2 l. of water), and the resulting solution heated to boiling. After filtration, the solution was warmed to 60° and 120 c.c. of 30% hydrogen peroxide in 1 l. of water were slowly added. After 2 hours, a further 120 c.c. of 30% hydrogen peroxide was added to the dark solution (at 60°). After 2 hours the solution was filtered and evaporated to 200 c.c. under diminished pressure. To the resulting syrup methanol (1600 c.c.) and ether (800 c.c.) were added. The precipitate formed was separated and the filtrate concentrated further to a thick syrup, which readily crystallised on standing at 0°. Yield of recrystallised D-arabinose, 51 g.; m. p. 155°; $[\alpha]_D^{18} - 105^\circ$ (c, 1.5 in water).

D-Arabinose (2 g.) was shaken with dry acetone (1 l.), anhydrous cupric sulphate (80 g.), and barium carbonate (10 g.) for 8 days at room temperature. The filtered solution was evaporated to dryness and the resulting syrup recrystallised from ether (0.2 g.); m. p. 78°; $[\alpha]_D^{19} - 111^\circ$ (c, 1.1 in water, no mutarotation) (cf. monoacetone L-arabinose, Ohle and Berend, *loc. cit.*; m. p. 76–77°; $[\alpha]_D + 128^\circ$). Treatment of this product with acetone and concentrated sulphuric acid yielded diacetone D-arabinose; m. p. 40–41° $[\alpha]_D^{19} - 4^\circ$ (c, 1.1 in water).

3:4-Monoacetone β -Methyl-D-arabinoside.—D-Arabinose (25 g.) was converted into the glycoside by being refluxed with methanolic hydrogen chloride (1%; 500 c.c.) for 10 hours. The β -form readily crystallised from a small amount of methanol; m. p. 168°. Yield, 12 g.

β -Methyl D-arabinose (2 g.) was shaken at room temperature with dry acetone (100 c.c.) and concentrated sulphuric acid (1.0 c.c.) for 72 hours. The acid was neutralised (litmus) by addition of anhydrous sodium carbonate. The filtered solution was evaporated to dryness, and the remaining syrup distilled in a high vacuum; b. p. 90° (vap. temp.)/0.3 mm.; n_D^{19} 1.4600 (Found: OMe, 9.2. Calc. for $C_9H_{14}O_5$: OMe, 8.9%).

β -Methyl-D-arabinoside (10 g.) or 3:4-monoacetone β -methyl-D-arabinoside (10 g.) was shaken for 24 hours with dry acetone (300 c.c.) and concentrated sulphuric acid (5 c.c.) at room temperature. After neutralisation with sodium carbonate the filtered solution was evaporated to dryness and distilled in a high vacuum. The distillate rapidly crystallised from ligroin; m. p. 41°; OMe content, nil (m. p. 41.5–43° for diacetone L-arabinose; Svanberg and Bergman, *loc. cit.*).

2-p-Toluenesulphonyl 3:4-Monoacetone β -Methyl-D-arabinoside.—3:4-Monoacetone β -methyl-D-arabinoside (0.2 g.) was dissolved in dry pyridine (7 c.c.) to which was added *p*-toluenesulphonyl chloride (0.8 g.). After 24 hours at room temperature the mixture was poured into water (200 c.c.), and the crude product which separated was recrystallised from alcohol (0.2 g.); m. p. 134° (Found: C, 53.3; H, 6.1; S, 9.3; OMe, 9.2. $C_{16}H_{18}O_7S$ requires C, 53.5; H, 6.15; S, 8.95; OMe, 8.65%).

2-Methanesulphonyl 3:4-Monoacetone β -Methyl-D-arabinoside.—3:4-Monoacetone β -methyl-D-arabinoside (0.3 g.) was dissolved in dry pyridine (10 c.c.) and treated with methanesulphonyl chloride (0.5 g.). After 48 hours the solution was poured into water (250 c.c.). No solid separated, and the aqueous solution was extracted several times with chloroform. The chloroform solution was washed with dilute hydrochloric acid and then with water and finally dried (Na_2CO_3). Evaporation of the resulting solution afforded a syrup which readily crystallised (0.2 g.) from alcohol; the compound had m. p. 135° (Found: OMe, 10.9. $C_{16}H_{18}O_7S$ requires OMe, 11.0%).

Attempted Formation of 2-Iodo 3:4-Monoacetone β -Methyl-D-arabinoside.—(i) 2-p-Toluenesulphonyl 3:4-monoacetone β -methyl-D-arabinoside (0.2 g.) was dissolved in dry acetone (20 c.c.) to which was added dry sodium iodide (2 g.). The mixture was heated at 110° for 12 hours in a sealed tube. The starting material (0.16 g.) was recovered unchanged.

(ii) 2-Methanesulphonyl 3:4-monoacetone β -methyl-D-arabinoside (0.5 g.) was heated with dry acetone (25 c.c.) and sodium iodide (2 g.) in a sealed tube at 110° or 130° for 48 hours. The starting material was recovered unchanged.

Methylation of 3:4-Monoacetone β -Methyl-D-arabopyranoside.—The monoacetone glycoside (0.7 g.) was heated for 6 hours with methyl iodide (5 c.c.) and silver oxide (1 g.). After 3 such methylations, the syrupy product was distilled; b. p. 136–137° (bath temp.)/2 mm. The distillate (n_D^{20} 1.4520) readily crystallised on standing, and after recrystallisation from acetone-ligroin the compound had m. p. 43°; $[\alpha]_D^{20} - 145^\circ$ (c. 1.8, in water) (Found: C, 55.1; H, 8.2; OMe, 28.2. $C_{16}H_{18}O_6$ requires C, 54.9; H, 8.3; OMe, 28.4%). Yield, 0.5 g.

Formation of 2-Methyl β -Methyl-D-arabopyranoside.—2-Methyl 3:4-monoacetone β -methyl-D-arabopyranoside (0.3 g.) was heated for 3 hours with methanolic hydrogen chloride (20 c.c.; 5%); $[\alpha]_D^{20} - 130^\circ \rightarrow -35^\circ$. The resulting solution was neutralised (litmus) with silver carbonate and the filtrate evaporated, giving a syrup, n_D^{20} 1.4602, which crystallised on standing (0.2 g.). After recrystallisation from methanol-ether the compound had m. p. 48° (Found: OMe, 31.6. $C_7H_{14}O_6 \cdot H_2O$ requires OMe, 31.6%).

2-Methyl D-Arabinose.—2-Methyl β -methyl-D-arabopyranoside (0.2 g.) was heated at 100° for 6 hours with sulphuric acid (N; 10 c.c.); $[\alpha]_D^{20} - 96^\circ \rightarrow -56^\circ$. The solution reduced Fehling's solution and was neutralised (phenolphthalein) with sodium hydroxide and evaporated, and the residue extracted with chloroform. On evaporation of the chloroform extract to dryness, 2-methyl D-arabinose was obtained as a reducing syrup (0.1 g.); n_D^{20} 1.4710 (Found: OMe, 18.6. $C_6H_{12}O_5$ requires OMe, 18.9%).

Treatment of this syrup with phenylhydrazine (3 drops), glacial acetic acid (4 drops), and water (2 c.c.) at room temperature for several hours afforded a crystalline phenylhydrazone which, after recrystallisation from aqueous ethanol, had m. p. 113° (Found: OMe, 12.2. $C_{12}H_{18}O_4N_2$ requires OMe, 12.2%).

Formation of 2-Methyl D-Arabinose p-Toluenesulphonylhydrazone.—2-Methyl D-arabinose (0.1 g.) was dissolved in absolute alcohol (8 c.c.), treated with *p*-toluenesulphonylhydrazine (Freudenberg and Blümmel, *Annalen*, 1924, 440, 51) (0.1 g.), and the mixture heated under reflux for 1 hour. On removal of the solvent, the *p*-toluenesulphonylhydrazone separated, and after recrystallisation from aqueous alcohol had m. p. 143° (decomp.); $[\alpha]_D^{16} - 17.0^\circ$ (c. 0.8 in water) (initial value) (Found: OMe, 9.1. $C_{13}H_{20}O_6N_2S$ requires OMe, 9.4%).

3:4-Monoacetone β -Methyl-L-arabinoside.—(a) β -Methyl-L-arabopyranoside (2 g.) was shaken with acetone (250 c.c.) and anhydrous copper sulphate (10 g.) for 7 days. The solution was then filtered and the filtrate concentrated under diminished pressure to a syrup (2 g.), n_D^{20} 1.4642.

(b) (Cf. Robertson and Speedie, *J.*, 1934, 824.) The arabinoside (2 g.) was shaken with acetone (20 c.c.) containing hydrogen chloride (2 g.) for 48 hours. The clear solution was then poured into excess of dilute sodium hydroxide solution and the product extracted thrice with chloroform. The chloroform solution was then dried (Na_2CO_3), filtered, and concentrated under reduced pressure to a syrup (1.8 g.) which was distilled; the compound had b. p. 105° (bath temp.)/0.01 mm.; n_D^{20} 1.4628 (Found: C, 52.9; H, 8.1. $C_6H_{12}O_5$ requires C, 52.9; H, 7.9%).

The corresponding 2-p-toluenesulphonyl derivative was prepared by reaction of 3:4-monoacetone β -methyl-L-arabinoside (4.0 g.) with *p*-toluenesulphonyl chloride (4.5 g.; 1.1 ml.) in dry pyridine (25 c.c.) at 40°. The warm solution was diluted with water and cooled, and the product filtered off and dried. Yield, 4.5 g.; m. p. 134° (Found: C, 53.8; H, 5.6; OMe, 8.6. $C_{16}H_{18}O_7S$ requires C, 53.6; H, 6.2; OMe, 8.7%). Hydrolysis of this product with boiling 50% acetic acid gave 2-p-toluenesulphonyl β -methyl-L-arabinoside in low yield as deliquescent crystals of low melting point. The product was not further examined.

2-Methyl 3:4-Monoacetone β -Methyl-L-arabopyranoside.—3:4-Monoacetone β -methyl-L-arabopyranoside (2 g.) was methylated with silver oxide and methyl iodide and the product distilled under reduced pressure. The corresponding 2-methyl ether distilled at 100° (bath temp.)/0.01 mm.; n_D^{20} 1.4481 (Found: C, 54.9; H, 8.3; OMe, 28.4. $C_{10}H_{18}O_6$ requires C, 55.1; H, 8.2; OMe, 28.4%).

2-Methyl β -Methyl-L-arabopyranoside.—2-Methyl 3:4-monoacetone β -methyl-L-arabopyranoside (1.86 g.) was boiled with water (20 c.c.) containing glacial acetic acid (5 c.c.) for 2 hours ($[\alpha]_D^{20} + 202^\circ$ initial value, $\rightarrow +186^\circ$). The solution was concentrated under reduced pressure to a syrup which was distilled in a vacuum; b. p. 130° (bath temp.)/0.01 mm.; n_D^{20} 1.4768. This product crystallised shortly after distillation; m. p. 59° (Found: C, 47.0; H, 8.2; OMe, 34.2. $C_7H_{14}O_6$ requires C, 47.2; H, 7.9; OMe, 34.8%). On recrystallisation from acetone-ether the arabinoside separated as the monohydrate, m. p. 47° (Found: C, 42.9; H, 7.7; OMe, 31.4. $C_7H_{14}O_6 \cdot H_2O$ requires C, 42.9; H, 8.2; OMe, 31.6%).

2-Methyl L-Arabinose.— β -Methyl 2-methyl-L-arabinoside (1.06 g.) was hydrolysed with boiling N-sulphuric acid (25 c.c.) for 4 hours; $[\alpha]_D^{20} + 234^\circ$ (initial value) $\rightarrow +99^\circ$ (constant value). The

cooled solution was neutralised with barium carbonate and filtered, and the filtrate evaporated under reduced pressure to a syrup which did not crystallise. With alcoholic phenylhydrazine crystalline 2-methyl L-arabinose phenylhydrazone was obtained, m. p. 116° after recrystallisation from alcohol-ether-light petroleum (Found : C, 56.8; H, 7.8; N, 10.9; OMe, 12.4. $C_{12}H_{18}O_4N_2$ requires C, 56.7; H, 7.1; N, 11.0; OMe, 12.2%). No crystalline anilide could be isolated.

On shaking an acetone solution with anhydrous copper sulphate 2-methyl L-arabinose gave 2-methyl monoacetone L-arabinose which, on evaporation of the filtered solution, was isolated as a crystalline reducing solid, m. p. 117°. It was purified by recrystallisation from acetone and sublimed in a vacuum (Found : C, 52.8; H, 7.8; OMe, 15.1. $C_8H_{14}O_5$ requires C, 52.9; H, 7.8; OMe, 15.2%).

On being heated with alcoholic aniline this product gave crystalline 2-methyl monoacetone L-arabinose anilide, m. p. 143° after recrystallisation from ethyl alcohol (Found : C, 64.4; H, 7.4; N, 4.8; OMe, 11.0. $C_{15}H_{21}O_4N$ requires C, 64.6; H, 7.4; N, 5.0; OMe, 11.1%).

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[Received, December 12th, 1946.]

248. The Quantitative Separation of Methylated Sugars.

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Two methods for the quantitative separation of fully methylated sugars from their partly methylated derivatives are described. The first is a standardised procedure for the quantitative chromatographic separation of methylated sugar glycosides on activated alumina by means of which quantities as small as 245 mg. of tetramethyl methylglucoside can be separated from a large excess of 2:3:6-trimethyl methyl- α -glucoside. In the second method the fully methylated sugar glycoside, which may weigh as little as 36 mg., can be recovered from admixture with a large excess of admixed partly methylated sugar glycosides by preferential extraction of the fully methylated derivative with light petroleum from water using two continuous extraction apparatuses, one fitted above the other.

DETAILED knowledge of structure in the carbohydrate group has been largely dependent upon the possibility of separating and identifying the various components of the mixture of methylated sugars obtained on hydrolysis of the methyl ethers of the materials under investigation. The quantitative aspect of this problem assumed special importance in the development of the chemical end group method applied by Haworth and Machemer (*J.*, 1932, 2270) in their determination of the chain length of cellulose. This involved the quantitative separation, by fractional distillation, of a very small amount of tetramethyl glucose from a larger amount of 2:3:6-trimethyl glucose, similar problems being met with in studies on starch and glycogen. Even in this comparatively simple case complications are encountered in the course of the fractional distillation of the mixture of methylated methylglucosides, and special methods had to be adopted in order to obtain accurate results (see Hirst and Young, *J.*, 1938, 1247; Averill and Peat, *ibid.*, p. 1244; Peat and Whetstone, *J.*, 1940, 276). In the course of attempts to overcome the difficulties inherent in the method of separation by distillation other procedures have been elaborated, including, for example, (a) phosphorylation of the partly methylated glycosides followed by extraction of the fully methylated glycoside from aqueous solution by organic solvents (Hess and Neumann, *Ber.*, 1937, 70, 710; Leckzyk, *ibid.*, 1938, 71, 829; Hess, Grigorescu, Steurer, and Forham, *Ber.*, 1940, 73, 505), and (b) separation of the sugars on silica (Bell, *J.*, 1944, 473), or chromatographic separation of the glycosides on alumina (Jones, *J.*, 1944, 333).

An outline of the method of separation of methylated sugar glycosides on alumina has already been given (Jones, *loc. cit.*). We have now standardised this method and find it so sensitive that even the α - and β -methylglucosides of tetramethyl glucopyranose may be separated partially one from another. The recovery of the sugars by this procedure amounts to 93% of the fully methylated sugar, so that a small correction is necessary in order to obtain the exact amount of end-group present.

A further method, which we have developed quantitatively on the semi-micro scale, depends upon the fact that fully methylated sugars are much more readily extracted from water with light petroleum (b. p. 38–40°) than are partly methylated sugars. Tetramethyl methylglucoside has a partition coefficient of about 10 between chloroform and water whilst the partition coefficient found for 2:3:6-trimethyl methylglucoside is about 2 between chloroform and water (cf. the work of Macdonald, *J. Amer. Chem. Soc.*, 1935, 57, 771, who determined the coefficient for the corresponding free sugars). We have found that the partition coefficient of fully methylated glucose between light petroleum (b. p. 38–40°) and water is about 0.1 whilst the correspond-

ing figure for trimethyl methylglucoside is <0.01 . The ratio between these last two figures is such that we were able to develop a method for the separation of the sugar derivatives by a continuous extraction process.

In carrying out the separation two continuous extractors are fitted, one above the other. In the top apparatus is placed the mixture of glycosides dissolved in water or sodium hydroxide solution, whilst the bottom apparatus initially contains water only. The apparatus is connected to a reservoir flask containing boiling light petroleum (b. p. 38–40°). The vapours are condensed and drop through the top solution and extract a mixture of sugars, mainly the fully methylated α - and β -glycosides; the extracts are then washed by passing through the water in the lower apparatus and finally return to the reservoir. This extraction is interrupted at intervals, solvent evaporated, the residual syrup weighed, and the refractive index determined. When a refractive index, combined with optical rotatory determination, shows the extract to be free from the fully methylated derivative (Hirst and Young, *loc. cit.*), the previous extracts are combined and dissolved in water, and the whole process is repeated in a similar apparatus. Eventually, following this technique, fractions consisting of fully methylated glycosides free from partly methylated sugars are obtained. In trial experiments the recovery of fully methylated sugar glycosides was of the order of 98–102%. By the use of this method the quantitative separation of the methylglucosides of 2:3:4:6-tetramethyl *d*-glucose and 2:3:6-trimethyl *d*-glucose (1:1 mixtures), and of 2:3:4:6-tetramethyl *d*-galactose and 2:3:6-trimethyl *d*-glucose (1:1 mixtures) has been achieved. This method has also been applied successfully to the quantitative separation of one part of tetramethyl methylglucoside (36 mg.) from 24 parts of partly methylated methylglucosides (865 mg.), and can be used with reasonable accuracy for still lower concentrations of the fully methylated sugar. These methods can therefore be applied to the determination of the size of the repeating unit of methylated polysaccharides. Since the partition method is applicable also to the quantitative separation of fully methylated pentose sugars from partially methylated pentose and hexose sugars, it can be used for the quantitative determination of the sugars formed on methanolysis of the complex methyl ethers of gums and mucilages; as an example of its utility the quantitative separation of the methylglycosides produced on hydrolysis of methylated peanut araban is described. The results obtained are in full agreement with those obtained by using the distillation procedure (Hirst and Jones, in the press).

Experimental difficulties may arise if the methylated polysaccharide is not rigorously purified before methanolysis, since any impurities present in it which are soluble in light petroleum will contaminate the fully methylated sugar finally obtained. In the event of a coloured and impure fraction of fully methylated sugar being isolated it may be purified by distillation in an apparatus of the type described by Ellis (*Chem. and Ind.*, 1934, 77). The loss during the final distillation is less than 1 mg. on quantities of the order of 40 to 100 mg. of tetramethyl methyl-*d*-glucoside.

EXPERIMENTAL.

As a result of many experiments with various solvents and weights of alumina the following technique was found to be the most satisfactory for the separation of tetramethyl α - and β -methyl-*d*-glucoside from a mixture of 2:3:4:6-tetramethyl methyl-*d*-glucoside and 2:3:6-trimethyl methyl-*d*-glucoside.

A solution of 2:3:4:6-tetramethyl α -methyl- (530 mg.) and β -methyl- (515 mg.) *d*-glucoside and 2:3:6-trimethyl methyl-*d*-glucoside (1.02 g., prepared from pure 2:3:6-trimethyl *d*-glucose) in light petroleum (b. p. 60–80°; washed with sulphuric acid and sodium hydroxide solution and distilled) was passed through a column of alumina (from the British Aluminium Co., Burntisland, Scotland, activated at 360° for 4 hours; 350 g., length 18 ins., cross section $1\frac{1}{4}$ ins.), and the column developed with chloroform [dried (CaCl₂) and distilled]. The eluate was collected in fractions (100 c.c.) each of which was tested for the presence of sugars by the Molisch test after withdrawing a sample (5 c.c.) and removing the solvent by evaporation. After the passage of chloroform (1100 c.c.), fractions of sugar were isolated having the following properties, all rotations being measured in chloroform solution: (1) 50 mg., n_D^{18} 1.4440, $[\alpha]_D^{18}$ +75°; (2) 60 mg., n_D^{18} 1.4436, $[\alpha]_D^{18}$ +110°; (3) 125 mg., n_D^{18} 1.4442, $[\alpha]_D^{18}$ +130°; (4) 90 mg., n_D^{18} 1.4437, $[\alpha]_D^{18}$ +83°; (5) 70 mg., n_D^{18} 1.4436, $[\alpha]_D^{18}$ +68°; (6) 105 mg., n_D^{18} 1.4420, $[\alpha]_D^{18}$ +20°; (7) 440 mg., n_D^{18} 1.4414 (superfused), $[\alpha]_D^{18}$ –25°. The syrup from this fraction crystallised; m. p. 37°. Total yield, 940 mg. (92% recovery). The next fractions gave a weak positive Molisch test but left no weighable residue of sugar on evaporation. The trimethyl methyl-*d*-glucoside was eluted with methyl alcohol. Yield, 1.0 g. Since the yield of fully methylated sugar which would be isolated from a partly methylated starch of weight 5 g. (an amount convenient to handle in methylation work) is about 240 mg., tetramethyl methylglucoside (245 mg., n_D^{18} 1.4440) and trimethyl methylglucoside (382 mg., n_D^{18} 1.4572) were separated. The sugars, dissolved in light petroleum (b. p. 40–60°, 50 c.c.), were passed through a column of activated alumina (18 ins. \times $1\frac{1}{4}$ ins.). The alumina was then eluted with alcohol-free, dry chloroform and the following fractions of sugars isolated on concentration of 100 c.c. portions of the chloroform eluate: Fraction A (28 mg.), n_D^{18} 1.4462; Fraction B (49 mg.), n_D^{18} 1.4460; Fraction C (51 mg.), n_D^{18} 1.4449; Fraction D (24 mg.), n_D^{18} 1.4440; Fraction E (54 mg.), n_D^{18} 1.4420; Fraction F (20 mg.), n_D^{18} 1.4415. This last fraction crystallised; m. p. of solid, 37°. Two further

fractions contained a negligible amount of sugar (<1 mg.)—thereafter trimethyl methylglucoside was eluted. This yield of sugars (Fractions A to F, 226 mg.) corresponds to a yield of 93%.

Since the yield of 2 : 3 : 4 : 6-tetramethyl methyl-*d*-glucoside was 92%, a correction is necessary when applying this method to the determination of the repeating unit of methylated starch or glycogen. The technique described above is applied to the separation of approximately equal parts of tetramethyl and trimethyl methyl-*d*-glucosides. To approximate to these conditions when carrying out a determination of the repeating unit of a polysaccharide it is necessary to carry out a preliminary enrichment of the "tetra" fraction present in the hydrolysis products from the methylated polysaccharides. This is carried out by the following general procedure. The methylated polysaccharide is hydrolysed by boiling with methanolic hydrogen chloride. After neutralisation of the solution, with silver carbonate, *N*-sodium hydroxide (slight excess), or diazomethane, and filtration if necessary, solvent is removed at 760 mm. on the water-bath and finally in a vacuum at 25°, and the residual syrup dissolved in water (ca. 50 c.c.) and extracted continuously with redistilled sulphur-free light petroleum in an all-glass apparatus for about 4 hours. This procedure usually removes all the fully methylated sugar from the aqueous solvents along with about an equal weight of trimethyl methylglucoside. To guard against incomplete extraction, the water solution is again extracted with light petroleum (b. p. 38–40°) for about 4 hours, and the extracts are added to the first extract. If the sodium hydroxide neutralisation technique is used, contamination of the fraction rich in fully methylated sugar with methyl lavulate is avoided. These extracts are then combined and concentrated, and the product is weighed and subsequently separated on the column as described above.

Quantitative Separation of Fully Methylated Sugars from Partly Methylated Sugars by Partition between Water and Light Petroleum (b. p. 38–40°).—The mixture of methylated methylglucosides is dissolved in dilute sodium hydroxide solution (to remove traces of acids and esters) and extracted continuously in an apparatus consisting of two all-glass continuous extraction vessels ("Quickfit" and Quartz/EX8/23) in series. The solution of sugars (40 c.c.) is placed in the top apparatus; the second extractor contains water (75 c.c.) which serves the purpose of washing the light petroleum extracts.

In a trial experiment fully methylated glucose ($n_D^{18} 1.4434$; 257 mg.) and trimethyl methylglucoside ($n_D^{18} 1.4572$; 223 mg.) were dissolved in water (40 c.c.) and extracted in the apparatus for 2½ hours. Concentration of the extract gave a syrup (235 mg.; $n_D^{18} 1.4434$; $[\alpha]_D^{20} +53^\circ$, in water). Further extraction for two hours gave a syrup (20 mg.; $n_D^{18} 1.4430$; $[\alpha]_D^{20} +40^\circ$, in water). Two further extracts of 2 hours each gave products (9 mg. and 12 mg.) which were trimethyl methylglucoside. Recovery is therefore 255 mg. or 99%.

In a second experiment tetramethyl methylglucoside (126 mg.; $n_D^{18} 1.4437$) and trimethyl methylglucoside (129 mg.; $n_D^{18} 1.4572$) were dissolved in water (50 c.c.) and extracted as before for 2½ hours. Concentration of the extract left a residual syrup (107 mg.; $n_D^{18} 1.4431$; $[\alpha]_D^{20} +38^\circ$). Further extraction for 2 hours gave a syrup (23 mg.; $n_D^{18} 1.4423$; $[\alpha]_D^{20} +14^\circ$). Continuation of the extraction (2 periods of 2 hours) gave on concentration a very small yield of syrup (1–2 mg.). Recovery of fully methylated glucose, 102%.

In the above two experiments the ratio of tetramethyl to trimethyl methylglucoside is about 1 : 1. With most polysaccharides, e.g., starches and celluloses, the proportion of end group is much less than this, and further experiments were carried out to test the accuracy of this method when applied to mixtures containing one part of tetramethyl methylglucoside to 19–34 parts of trimethyl methylglucoside. Fully methylated glucose (140 mg.; $n_D^{18} 1.4438$) and trimethyl methylglucoside (2577 mg.; $n_D^{18} 1.4574$) were dissolved in water (50 c.c.) and extracted for 5 hours. Concentration of the extract left a syrup (C) (347 mg.; $n_D^{18} 1.4510$). Further extraction with light petroleum gave a syrup (93 mg.; $n_D^{18} 1.4550$) which contained no fully methylated glucose since on extraction in the same way for 5 hours it yielded trimethyl *d*-methylglucoside (7 mg.) only. Accordingly the extract (C) (347 mg.) was dissolved in water (50 c.c.) and extracted once again for 5 hours. Yield of syrup, 138 mg.; $n_D^{18} 1.4434$; $[\alpha]_D^{20} +60^\circ$ (in water). Further extraction for two hours gave the partly methylated glucose (16 mg.), $n_D^{18} 1.4562$. Recovery of fully methylated glucose is therefore 138 mg. (98.5%).

In another experiment a mixture of tetramethyl (53 mg.; $n_D^{18} 1.4438$) and 2 : 3 : 6-trimethyl methyl-*d*-glucoside (1715 mg.; $n_D^{18} 1.4574$) and 2 : 3-dimethyl methylglucoside (157 mg.; m. p. 79°) were put through this double procedure which resulted in a recovery of 98% of the fully methylated sugar (52 mg.; $n_D^{18} 1.4441$; $[\alpha]_D^{20} +80^\circ$).

In a further experiment a mixture of tetramethyl methylglucoside (36 mg.; $n_D^{18} 1.4440$), 2 : 3 : 6-trimethyl methylglucoside (865 mg.; $n_D^{18} 1.4582$), and 2 : 3-dimethyl methylglucoside (26 mg.; m. p. 79°) was extracted in the same way and gave a recovery of the fully methylated sugar of 100% (36 mg.; $n_D^{18} 1.4441$; $[\alpha]_D^{20} +80^\circ$ in water).

Separation of Tetramethyl Methylgalactoside and 2 : 3 : 6-Trimethyl Methylglucoside.—Heptamethyl methyl-lactoside (199 mg.; m. p. 77–79°) was dissolved in boiling methanolic hydrogen chloride (25 c.c.; 1%) and hydrolysed by boiling the solution for 8 hours. The solution was then neutralised with *N*-sodium hydroxide and concentrated in a vacuum to a syrup which was dissolved in water (50 c.c.) and extracted continuously with light petroleum (b. p. 38–40°) in the standard apparatus. Continuous extraction of the aqueous solution for 9 hours gave tetramethyl methylgalactoside [105 mg. (96%); $n_D^{18} 1.4492$] on concentration of the extracts. Further extraction for 3 hours gave, on removal of the solvent, < 3 mg. of syrup. The syrup (105 mg.) was hydrolysed with boiling *N*-hydrochloric acid, and the syrupy 2 : 3 : 4 : 6-tetramethyl *d*-galactose isolated in the usual manner and identified by conversion into the corresponding crystalline anilide, m. p. and mixed m. p. with an authentic specimen, 190°. The aqueous solutions remaining in the apparatus were then combined and extracted continuously with chloroform. Removal of the solvent left 2 : 3 : 6-trimethyl methylglucoside [102 mg. (98%); $n_D^{18} 1.4574$], identified after hydrolysis with boiling *N*-hydrochloric acid as 2 : 3 : 6-trimethyl *d*-glucose.

Separation of the Hydrolysis Products of Methylated Peanut Arabin.—(a) Methylated peanut arabin (4.4 g.) was boiled with methanolic hydrogen chloride (1%; 100 c.c.) during 7 hours. The cooled solution was neutralised with silver carbonate and filtered. The filtrate on concentration gave a mixture of glycosides (5.2 g.) which was fractionated. A portion of this syrupy product (1.519 g.) was dissolved in water

(50 c.c.) and extracted continuously in a double extractor with purified light petroleum (b. p. 38–40°). The following fractions were obtained: Fraction 1 (0.498 g.), n_D^{20} 1.4380; Fraction 2 (0.039 g.), n_D^{20} 1.4439; Fraction 3 (0.53 g.), n_D^{20} 1.4510. Fractions 1 and 2 contained 0.517 g. of trimethyl methyl-*l*-arabinoside corresponding to a yield of 32% (calculated on the weight of glycosides) (Found by the distillation method: 32.2%).

(b) A further portion of the methanolysis product (1.31 g.) of methylated peanut araban was dissolved in water (50 c.c.) and extracted continuously in a double extractor as described above. The following fractions were isolated: 2:3:5-Trimethyl methyl-*l*-arabinoside (0.42 g.), n_D^{18} 1.4390 (Found: OMe, 59.7. Calc. for $C_6H_{14}O_5$: OMe, 60.2%); 2:3-dimethyl methyl-*l*-arabinoside (0.40 g.), n_D^{18} 1.4530 (Found: OMe, 48.2. Calc. for $C_6H_{14}O_5$: OMe, 48.4%). The residual aqueous solution on concentration gave 2-methyl methyl-*l*-arabinoside (0.46 g.), n_D^{18} 1.4749 (Found: OMe, 37.2. Calc. for $C_7H_{14}O_5$: OMe, 34.8%). Total recovery of sugars, 98%. These figures indicate that trimethyl, dimethyl, and monomethyl methyl-*l*-arabinoside were present after methanolysis in equimolecular proportions.

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice and the British Cotton Industry Research Association for the award of a Shirley Fellowship to one of them (F. B.).

THE UNIVERSITY OF MANCHESTER.

[Received, December 13th, 1946.]

249. Qualitative Semimicro-analysis with Reference to Noyes and Bray's System: Partial Analysis of the Combined Nickel, Zirconium, and Rare-earth Groups.

By CHRISTINA C. MILLER.

A scheme of analysis is presented for the detection and approximate determination of 0.25–50 mg. of manganese, cobalt, or nickel, 0.25–10 mg. of titanium, zirconium, indium, or scandium, and a small amount of zinc (minimum 0.25 mg.) in solutions containing a maximum of 50 mg. referred to the metals. These include all the more important elements present in the combined nickel, zirconium, and rare-earth groups of Noyes and Bray's scheme. The maximum amount of any one rare-earth group metal is 10 mg. In separate portions of the solution, manganese, cobalt, nickel, titanium, and zirconium are detected, respectively, by means of potassium periodate, ammonium thiocyanate and extraction with butyl acetate, dimethylglyoxime, chromotropic acid, and *p*-hydroxyphenylarsonic acid. In a sixth portion zinc is separated from cobalt and more than 1 mg. of nickel, and tested for with copper sulphate and ammonium mercury thiocyanate. Finally, in a seventh portion indium and scandium are isolated. Indium is precipitated as indium sulphide and confirmed with alizarin, and scandium detected by means of alizarin-S or morin.

SCHEMES for the analysis on a semimicro-scale of seven groups of Noyes and Bray's system ("A System of Qualitative Analysis for the Rare Elements," 1927) have already been reported by Miller and Lowe (*J.*, 1940, 1258, 1263) and Miller (*J.*, 1941, 72, 786; 1943, 72). This paper describes the further application of semimicro-analytical methods to the detection of manganese, cobalt, nickel, zinc, titanium, zirconium, indium, and scandium in a group containing all the more important metals associated with the nickel, zirconium, and rare-earth groups of Noyes and Bray's scheme.

After removing metals precipitable by hydrogen sulphide in acid solution, Noyes and Bray precipitate those of the ammonium sulphide group in two separate operations. From one precipitate iron, gallium, and components of the aluminium group are eliminated, leaving indium, zirconium, and titanium (zirconium group), some rare-earth group metals, and traces of cobalt, nickel, and zinc. From the other precipitate components of the aluminium group are removed, leaving manganese, cobalt, nickel, and a little zinc (nickel group), and some rare-earth group metals. In the course of analysis of the second precipitate the rare-earth group portion is separated and added to the first precipitate, from which the whole rare-earth group (scandium, thorium, yttrium, lanthanum, cerium, etc.) is extracted before the zirconium group proper is analysed. A variable amount of indium is located in the rare-earth group so that the metal has to be tested for twice.

The method of analysis used here is entirely different. It is supposed that the above precipitates are dissolved in hydrochloric acid and the solutions combined to give a mixture inclusive of all the components of Noyes and Bray's three groups. The mixtures considered here may contain any of *e.g.*, manganese, cobalt, nickel, titanium, zirconium, zinc, indium, scandium, thorium, yttrium, cerium, lanthanum, neodymium, and praseodymium. In portions of them the first five, and sometimes zinc, are tested for directly. Indium and scandium, and zinc in certain circumstances, are detected after they have been freed from interfering elements. In this connection organic solvents as extractants play an important part. As

in earlier papers the experimental conditions described permit the detection of the above metals in accordance with the limits set forth in the summary. Provision is made for the presence of group contaminants, *e.g.*, iron, gallium, and members of the aluminium group. Because of scarcity of material the question of the detection of hafnium, which behaves like zirconium, has not yet been considered, and other rare-earth metals have not been taken into account.

Particulars regarding the isolation of the rare-earth group of metals from one half of the above mixtures, and the subsequent analysis of the group, will, it is hoped, be given later.

EXPERIMENTAL.

Preparation of the Group for Analysis.—Mixtures containing chlorides or nitrates of the various metals and some hydrochloric acid were evaporated just to dryness and taken up in 1 ml. of 6*N*-hydrochloric acid.

Nickel, Zirconium, and Rare-earth Groups.

(The figures in parentheses are referred to in "Notes on Methods and Tests.")

Solution.—Contains cobalt, manganese, nickel, titanium, zirconium, zinc, indium, scandium, thorium, yttrium, lanthanum, cerium, neodymium, and praseodymium as chlorides in 1 ml. of 6*N* hydrochloric acid. Test separate portions as follows:

(a) Test 1% for Co in a test-tube ($\frac{3}{8}$ " \times 3"). Make 0.15 ml. of solution, 2*N* in HCl, add 10–20 mg. of NH_4F and NH_4SCN in large excess. Add 0.2 ml. of *n*-butyl acetate and shake briskly. A blue colour in the ester shows **Co**. Increase the ester to a maximum of 2 ml. when much Co is present. Compare with standards. (1.)

(b) Test 1% for Mn in a 5-ml. beaker. Add 0.05 ml. of H_3PO_4 (88%) and expel HCl by evaporating on the hot-plate. Then add 1 ml. of 2*N*- HNO_3 and 10 mg. of KIO_4 , and keep the solution at the boiling point in the covered beaker for at least 15 mins., keeping the volume constant by additions of water. A purple colour shows **Mn**. Centrifuge if necessary and compare with standards. (2.)

(c) Test 1% for Ni in a 0.5-ml. centrifuge tube. Add 0.1 ml. of 12% aqueous citric acid and 0.05 ml. of ammonia (*d* 0.88). Heat to 80°, add 0.05 ml. of 5% aqueous dimethylglyoxime (Na salt)—allow more for Co (0.1 ml. per 0.5 mg.)—stir thoroughly, and heat further for 1 min. If a red precipitate due to **Ni** appears, ensure complete precipitation, then centrifuge without cooling, separate the precipitate, dissolve it in 2*N*-HCl, and reprecipitate as before. Compare with standards. (3.)

(d) Test 0.25–1% for Ti on a spotting tile. Add 0.04 ml. of 0.2*M*- SnCl_2 in *N*-HCl and 0.05 ml. of 1% chromotropic acid in concentrated H_2SO_4 . Compare a violet colour, which shows **Ti**, with standards. (4.)

(e) Test 5% for Zr in a 1-ml. centrifuge tube. Make 0.25 ml. of solution, 4*N* in HCl, add 0.05 ml. of perhydrol if Ti is present, heat, and add 0.1 ml. of 4% aqueous *p*-hydroxyphenylarsonic acid. Heat in boiling water for 2 mins. and centrifuge. If a precipitate is present, separate it and add 0.05 ml. of perhydrol and 0.1 ml. of 2*N*-NaOH. Stir up, centrifuge, separate $\text{Zr}(\text{OH})_4$, and dissolve it in 0.1 ml. of 10*N*-HCl and 0.1 ml. of water. Treat with *p*-hydroxyphenylarsonic acid as before. A white precipitate shows **Zr**. Centrifuge and compare with standards. (5.)

(f) Test 10% for Zn. (i) Co absent, Ni < 100 μg . Make 0.25 ml., *N* in HCl, in a 0.5-ml. centrifuge tube, add 0.01 ml. of 0.01*M*- CuSO_4 and 0.1 ml. of ammonium mercury thiocyanate reagent (30 g. of HgCl_2 and 33 g. of NH_4SCN in 100 ml. of water). Stir briskly and centrifuge. A black or violet precipitate shows **Zn** which should be compared with standards. (6.)

(ii) Ni > 100 μg ., and/or Co present. Make 0.5 ml., 2*N* in HCl, in a "Pyrex" test-tube ($\frac{3}{8}$ " \times 3"), add a large excess of NH_4SCN and 100 mg. of NH_4F , and extract twice with 1 ml. of *n*-butyl acetate. Evaporate the combined extracts, with the aid of an air current, in a "Pyrex" test-tube placed in boiling water. Next cautiously decompose the thiocyanates with concentrated HNO_3 , and finally heat in a flame (air current still flowing) until all volatile products are expelled.

If Co is absent, dissolve the residue in 0.25 ml. of *N*- HNO_3 and test for Zn as in (i). If < 500 μg . of Co is present, add 0.2 ml. of water, 0.2 ml. of 2*N*-NaOH, and a drop of 3% H_2O_2 , boil, centrifuge, remove the solution, and add to it 0.04 ml. of concentrated HNO_3 . Test for Zn as in (i).

If > 500 μg . of Co is present, add to the residue 0.1 ml. of water and just enough 10% aqueous KCN to convert Co into a soluble complex. Add 1 drop of perhydrol and boil for a few mins. to form cobalticyanide. Then add glacial acetic acid in 20% excess by volume, and 0.05 ml. of 10% aqueous potassium cobalticyanide, and heat. If a turbidity appears heat further to coagulate. Separate and wash the precipitate, which may be zinc cobalticyanide, without stirring it up, in 2*N*-acetic acid. To confirm Zn add to the precipitate 0.05 ml. of 4*N*- H_2SO_4 , heat until fumes of H_2SO_4 appear and the precipitate is dissolved, and proceed with the removal of Co and the final test for Zn as above. (7.)

(g) Test 10% for In and Sc in a test-tube ($\frac{3}{8}$ " \times 3"). Add 0.05 ml. of 10*N*-HCl, 0.05 ml. of water, and 0.3 ml. of 10% aqueous cupferron. Extract thrice with 1 ml. of chloroform. To the residual aqueous layer add a large excess of NH_4SCN and extract twice with 1 ml. of *n*-butyl acetate. Wash the combined extracts with 0.05 ml. of 2*N*-HCl, saturated with NH_4SCN . Expel the ester, destroy thiocyanates, and remove volatile products as described under (f, ii). Dissolve the residue in 0.15 ml. of water, make approximately neutral, and add sufficient 10% aqueous KCN to convert Co and Zn into soluble complexes. Add a drop of perhydrol, boil, add a few drops of 2*N*-NaOH, and reboil for a short time. If a precipitate [$\text{In}(\text{OH})_3$ and $\text{Sc}(\text{OH})_3$] appears, separate it, wash it with hot water, and dissolve it in 0.5 ml. of 2*N*-acetic acid. (8.)

(i) Test for In. Into the hot solution pass H_2S for 10 mins. A yellow precipitate shows **In**. Centrifuge and determine it. If desired, confirm a small precipitate, after washing it, with alizarin. (9.)

(ii) Test for Sc in the centrifugate from In_2S_3 . H_2S must be absent for test (9).

(a) To 0.25 ml. of 2*N*-acetic acid add 0.01 ml. of 1% aqueous alizarin-S and 0.05 ml. of the test

solution, and set aside for 5 mins. If no pink colour is, observed add more test solution gradually up to a maximum of 0.25 ml., and more reagent if necessary. If a pink colour due to **Sc** appears readily, add additional reagent gradually. Should the colour become too deep a red, repeat the experiment with less of the test solution. Compare with standards. Allow 20 mins. for full colour development. (10.)

(β) To 0.25 ml. of 2*N*-acetic acid add 0.01 ml. of morin (0.02% in acetone) with which **Sc** shows a green fluorescence in ultra-violet light. Gradually add the test solution, up to a maximum of 0.25 ml. if necessary, until a match is obtained with a standard containing between 1 and 50 μg. of **Sc**. (11.)

(h) Reserve 50% for the isolation of the rare-earth group.

Notes on Methods and Tests.—The experimental technique has been described in earlier papers of the series.

Note 1. The amount of ammonium thiocyanate was such that some remained undissolved throughout the extraction process. The ammonium fluoride masked titanium (0.5 mg.) and group contaminants, *e.g.*, iron, vanadium, and uranium. 0.5 μg. of cobalt was detectable in 0.2 ml. of ester. The extraction of cobalt was highly efficient, and 2 ml. of ester were used merely when the colour was otherwise too dark for matching purposes. The detection of 1 μg. of cobalt was not affected by the presence of at least 1 mg. of any of its associates, or of any member of the aluminium group (Al, Be, Cr^{VI}, W^{VI}, U^{VI}, V^V), or of iron or gallium. Cobalt was not retained by the precipitated fluorides of the rare-earth metals.

Note 2. The limit of identification of manganese was 0.5 μg., and 50 μg. was the maximum desirable for the comparison of colours. The solution could be further diluted with water. 2 μg. of manganese were found in association with 1 mg. of any of the elements mentioned in Note 1, except chromium (VI), of which only 100 μg. were permissible without the preparation of a blank experiment. Phosphate precipitates deposited by titanium, zirconium, and cerium, especially the last, tended to retain a little manganese.

Note 3. Ammonium citrate held all the metals in solution. 0.5 μg. of nickel was detectable. Excess of dimethylglyoxime commonly separated out from cold solutions without seriously affecting estimations. Nickel was detectable in association with at least a 1000-fold excess of the metals cited in Note 1, including cobalt, if sufficient reagent was present. Iron and cobalt together may form a brown precipitate with dimethylglyoxime. 25 μg. of iron, which is much more than one would expect to have here, did not upset the detection of 1 μg. of nickel in the presence of 1 mg. of cobalt, if prolonged boiling was avoided. Reprecipitation of the nickel complex corrected for a marked diminution in the bulk of the precipitate, caused by other metals and especially cobalt.

Note 4. The final concentration of 50% sulphuric acid was chosen because, at lower concentrations, the sensitivity of the test was reduced, and, at much higher concentrations, the chromotropic acid itself gave too pronounced a colour, probably because of impurity. Stannous chloride prevented or reduced the interference of iron, vanadium, tungsten, and uranium. 0.5 μg. was just detectable, and 25 μg. were set as a maximum for determinations and for the amount of reagent recommended. Colours did not deteriorate within two hours. 2 μg. of titanium were detectable in the presence of at least a 1000-fold excess of any component of the group, or of aluminium, beryllium, gallium, or zinc; and 5 μg., with a 100-fold excess of chromium, iron, uranium, or vanadium, or a 10-fold excess of tungsten.

Note 5. This test was used for the detection of zirconium in the tantalum group. Precipitation was best effected in a solution 2–5*N* in hydrochloric acid, and 1 μg. of zirconium was just detectable. The maximum amount of titanium under consideration was held adequately in solution by perhydrol, provided that heating was not prolonged. The titanium complex, if inadvertently deposited, was readily soluble in a drop of hydrochloric acid and a drop of perhydrol, whereas even a small precipitate of the zirconium complex remained undissolved. Other metals in the solution might reduce the bulk of the complex. The reprecipitation process prevented under-estimation, and at the same time eliminated any titanium that might have been carried down. 5–10 μg. of zirconium were found in association with 100 times the amount of titanium. 2 μg. were detectable in the presence of at least a 1000-fold excess of any other group component, and also of iron, gallium, aluminium, beryllium, chromium, uranium, or vanadium.

Note 6. Zinc was detected in the aluminium group by this method. Nitric acid solutions are said to give superior results, but tests made in hydrochloric acid solution were very satisfactory also, 2 μg. of zinc being found. 10 μg. of zinc were detectable in association with at least a 100-fold excess of scandium, and a 500-fold excess of manganese, indium, zirconium, gallium, iron (more reagent needed), or rare-earth group metals. Only a 100-fold excess of titanium, which hindered the deposition, was permissible. Nickel greatly hindered the precipitation and a 5-fold excess only could be tolerated. Cobalt reacted with ammonium mercury thiocyanate and, in the presence of copper sulphate, violet and black precipitates like those for zinc might be obtained. Consequently cobalt had to be completely removed before zinc was tested for.

Note 7. The extraction of cobalt and zinc from thiocyanate–fluoride solutions by means of *n*-butyl acetate was essentially complete, and practically nothing except a little indium accompanied them, even when the maximum amounts of other metals were present. After the destruction of thiocyanates, and when cobalt was absent, the direct test for zinc was applicable. Experiments made with 25 μg. of zinc in association with varying amounts of cobalt showed that the separation of 0.5 mg. of the latter by means of sodium hydroxide involved the loss of 40% of the zinc. When, therefore, more than 0.5 mg. of cobalt was present it was converted into cobaltcyanide, and zinc precipitated as zinc cobaltcyanide. As a precipitate might be produced by traces of other metals, it was essential to dissolve it, separate cobalt, and test for zinc as above. In mixtures containing in addition to 25 μg. of zinc, 5 mg. of cobalt, nickel, manganese, or rare-earth group metals, or 1 mg. of each of titanium, zirconium, indium, and scandium, the amounts of zinc retrieved were 12, 10, 10, 20, and 25 μg., respectively. The low results were attributed to difficulty in recovering all the zinc cobaltcyanide, which was very finely divided and separated extremely slowly.

Note 8. For indium and scandium no direct tests applicable in the presence or any or all of the group components were found. The tests for scandium required the absence of a great many elements, and that for indium, a considerable number. The series of simple operations prescribed separated indium and scandium, with comparatively little loss, from all the other members of the group and likely contaminants. For instance, cupferron and chloroform eliminated titanium, zirconium, iron, gallium, vanadium, and some rare-earth metals (Lundell and Hoffman, "Outlines of Methods of Chemical Analysis," 1938, 118). The butyl acetate extract contained indium, scandium, zinc, and cobalt, and contaminants, *e.g.*, aluminium, beryllium, uranium, and tungsten. By means of potassium cyanide and sodium hydroxide all of these except indium and scandium, which were precipitated as hydroxides, were taken into solution.

Note 9. The above separation of indium and scandium was so satisfactory that the precipitation of indium sulphide sufficed for the detection of the element, 5 $\mu\text{g.}$ being readily found. For a doubtful test [precipitate too pale (ZnS), or discoloured (CoS)] confirmation by means of alizarin (Wenger, *Helv. Chim. Acta*, 1945, 28, 539) is recommended. The hydrochloric acid solution of the precipitate is spotted on drop-reaction paper which has been impregnated with alizarin (0.2% in alcohol), and the spot developed over concentrated ammonia. The paper is then momentarily dipped in 10% aqueous potassium cyanide and finally soaked in saturated aqueous boric acid. Indium leaves a violet-pink spot. The cyanide destroys colours initially produced by zinc and cobalt.

Note 10. The test with alizarin-S (Beck, *Mikrochim. Acta*, 1937, 2, 9) must be made in a weakly acid solution. The colour develops slowly and its depth varies with the acid concentration. In 2*N*-acetic acid interference from rare-earth metals is prevented, and that from other metals minimised. Indium did not itself react but, in the presence of scandium, it intensified the colour. The limit of identification of scandium was 2 $\mu\text{g.}$, and amounts in excess of 25 $\mu\text{g.}$ gave too deep colours for determination. 25 $\mu\text{g.}$ of scandium required fully 0.1 ml. of the reagent. An excess is undesirable because of its own colour.

Note 11. This test was described by Beck (*loc. cit.*). Under the prescribed conditions 1 $\mu\text{g.}$ of scandium was detectable. For determinations the upper limit was 50 $\mu\text{g.}$ Many other elements fluoresced, *e.g.*, thorium, zirconium, yttrium, indium, gallium, aluminium, beryllium, and zinc. A few quenched the fluorescence of scandium. The method of isolating scandium was, however, so satisfactory that the brightest fluorescence noted in mixtures containing 5 mg. of other elements, and no scandium, corresponded to <2 $\mu\text{g.}$ of scandium.

Analysis of Mixtures.—Eight mixtures were analysed in order to test the validity of the scheme. All contained, in addition to the normal group components, 0.5 mg. of each of iron, gallium, aluminium, and vanadium as contaminants. No. 5 contained 40 mg. of rare-earth group metals (Th, Y, Ce, La, and Pr); No. 7, 8 mg. of thorium and 1 mg. of lanthanum; and No. 8, 1 mg. of yttrium. The results shown in the table are the estimated weights in mg. of the metals found. Where these differed from the weights taken, the latter are shown in parentheses.

	Co.	Ni.	Mn.	Zn.	Ti.	Zr.	In.	Sc.
1	33 (44)	0.2 (0.25)	0	0.1 (0.25)	0.2 (0.25)	0.7 (1)	0	0.1 (0.25)
2	0.25	0.25 (0.5)	34 (28)	1 (2)	0.4 (0.5)	3 (4)	0.4 (0.5)	0.5
3	5 (6)	14 (12)	6 (7)	0	2.5 (4)	8 (9)	7 (6)	3 (4)
4	0.5	0	0.4 (0.5)	0	0	0.5	0.5 (1)	5 (7)
5	1.75 (1)	1.5 (2)	3	0.15 (0.25)	6	0	0.3 (0.5)	0.15 (0.25)
6	0	1.75 (1)	0	0	1	0	7 (10)	0.5 (1)
7	43 (32)	0	0.25	0.5 (1)	0	0	0	0
8	0	27 (36)	0.7 (1)	1 (0.5)	1 (0.5)	0.2 (0.25)	0.2 (0.25)	0

The results were considered satisfactory, and all the tests, except that for zinc in the presence of much cobalt, were expeditiously carried out. It would be a great advantage if one had a sensitive test applicable to the detection of zinc in these circumstances.

I am indebted to the Trustees of the Moray Fund for a Grant which has been used for the purchase of highly purified chemicals.

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[Received, December 16th, 1946.]

250. *Magnetic Studies on Polymerisation. Part I. Magnetic Optical Rotatory Powers and Diamagnetic Susceptibilities of Certain Polymethyl Methacrylates.*

By (Miss) M. E. BEDWELL.

The magneto-optic rotatory powers and diamagnetic susceptibilities of methyl methacrylate and the polymethyl methacrylates have been measured. The results may be employed to calculate the average molecular weights of the polymers, fair agreement being obtained with values determined by a viscosity method (Schulz and Blaschke).

THE magnetic susceptibility method which Farquharson (*Trans. Faraday Soc.*, 1936, 32, 219) employed to investigate the degree of polymerisation of 2:3-dimethylbutadiene and other substances, is used in the present investigation on the polymethyl methacrylates. In addition,

another method of molecular weight determination is proposed, which is based in the magneto-optical rotatory powers of the polymers concerned.

Melville and others (General Discussion, *Trans. Faraday Soc.*, 1944, **40**, 217—273) have surveyed the end-group, osmotic, and viscosity methods for the determination of the molecular weight of higher polymers; of these, Schulz and Dinglinger (*J. pr. Chem.*, 1940, **157**, 15), Schulz and Blaschke (*Z. physikal. Chem.*, 1942, *B*, **51**, 75), Baxendale, Bywater, and Evans (*J. Polymer Sci.*, 1946, **1**, 237), and Walling and Briggs (*J. Amer. Chem. Soc.*, 1946, **68**, 1141) have shown that the viscosity method can be usefully employed to find the molecular weights of the polymethyl methacrylates, using modifications of the Staudinger equation; the present results are compared with those obtained by Schulz and Blaschke in their detailed study of the benzoyl peroxide-catalysed polymerisation of methyl methacrylate.

Magnetic Optical Rotatory Powers.—Perkin (J., 1884, **45**, 421 *et seq.*) deduced from measurements on many homologous series of organic compounds that the molecular magnetic rotation M of a substance could be expressed by

$$M = S + n\Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Δ is the increase in rotation between successive members of an homologous series (the "CH₂ increment") which Perkin found experimentally to have a mean value of 1.023; n is the number of carbon atoms in the molecule; S is the "series constant" which Perkin obtained by subtracting the value of $n\Delta$ from the total observed rotation, the resulting figure being approximately constant for an homologous series of compounds and different for different series.

It was proposed to make use of this relationship in the estimation of molecular weights of higher polymers.

It follows from the above equation that a monomer is related to its polymer thus :

[illegible]

where M_p , M_m are the molecular magnetic rotations of polymer and monomer respectively, n_a is the average number of units in the molecule of polymer, and S_1 is the "series constant", which is in this case Perkin's constitutive correction for the formation of a new bond.

By definition,

$$M_p = \theta_p w_p / w; \quad M_m = \theta_m w_m / w$$

$$\theta_p = \alpha_p d / \alpha d_p; \quad \theta_m = \alpha_m d / \alpha d_m$$

where α_p , α_m , α are the observed rotations of polymer, monomer, and water respectively under the same conditions; θ_p , θ_m are the specific rotations of polymer and monomer, respectively; w_p , w_m , w are the molecular weights of polymer, monomer, and water, and d_p , d_m , d are the corresponding densities measured at the same temperature.

But $w_n = n_a \times w_m$, therefore

$$\theta_p n_a w_m / w = n_a \theta_m w_m / w + (n_a - 1) S_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Hence n_a may be calculated from the experimental results.

Diamagnetic Susceptibilities.—Farquharson's expression for the mass susceptibility of a polymer is

$$\chi_s = [n_a \chi_B + (n_a - 1)\lambda] / n_a v_m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where w_m is the molecular weight of the monomer, χ_s is the mass susceptibility of the polymer, χ_B is the molecular susceptibility of the monomer, n_a is the degree of polymerisation, and λ is Pascal's constitutive correction constant for the bond ruptured. This equation is used for the calculation of n_a .

Average Molecular Weights.—The following table has been drawn up from measurements of magneto-optic rotatory powers and diamagnetic susceptibility which are listed later (Tables I and II); t is the polymerisation time; n_a is the average number of units in the molecule of polymer, and w_p the corresponding average molecular weight, calculated from equations (3) and (4).

t (mins.).	Magneto-optic rotation.			Diamagnetic susceptibility.		
	n_a .	$n_a \beta_p$.	w_p .	n_a .	$n_a \chi_a$.	w_p .
0	1	1.093	100	1	0.5370	100
15	2	2.088	190	1—2	0.7521	130
30	2—3	2.535	240	2—3	1.248	220
45	4	4.279	410	3—4	2.192	380
60	5	5.556	550	5	2.904	500
75	14	13.77	1390	14	8.809	1380
180	68	66.80	6750	61 *	36.06	6110
				61 *	36.06	6110

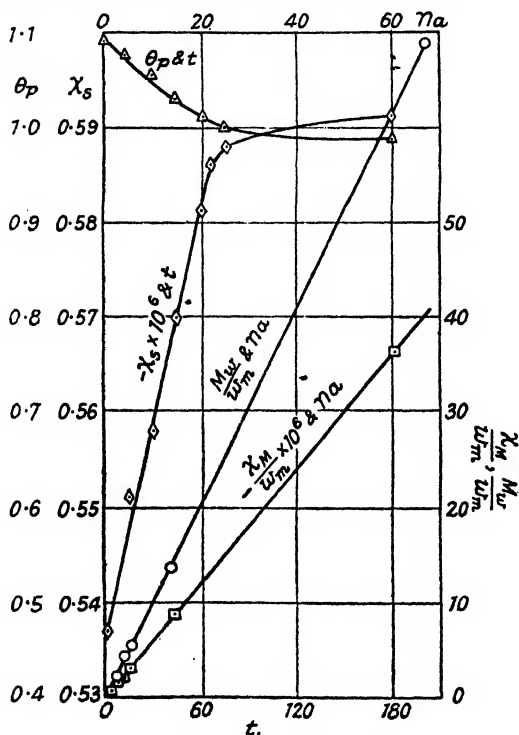
* Measurements on powder and solution, respectively.

A value of -1.112 was used for S_1 in equation (3), by analogy with ethyl crotonate, for which Perkin found an increase of rotation of 1.112 compared with ethyl butyrate; λ was assumed to be $+5.5$, which is Pascal's constitutive correction for the double bond.

The decrease in magneto-optic rotation and the increase in magnetic susceptibility which are found experimentally during polymerisation (Tables I and II) would be expected from the sign of the constants S_1 and λ above.

It will be seen that the figures for n_a and w_p obtained by the two methods agree very closely.

Extrapolation of the data of Schulz and Blaske to 80° and the benzoyl peroxide concentration used in the present investigation gives an upper limit of 5000–6000 for the molecular weight from viscosity measurements. Walling and Briggs quote higher figures in their determinations on benzoyl peroxide-free quinol-stabilised methyl methacrylate, and by analogy, an upper limit of 7000–8000 for the molecular weight may be estimated. The present figures (6750, 6110) are of the same order as the above, but from the calculation employed, it is obvious that decreasing accuracy is possible with polymers of molecular weights of the order 10^6 or higher.



Walling and Briggs found that, at 131° , concentrations of quinol of less than 1% had little effect on the molecular weight of the polymer, and it is doubtful whether the present concentration (0.03%) would cause alteration of the molecular weight to any appreciable extent at 80° .

Complete agreement is not to be expected, since both the present methods give the number-average molecular weight w_n , whereas the viscosity method gives the weight-average molecular weight w_w :

$$w_n = \Sigma w_i N_i / \Sigma N_i \text{ and } w_w = \Sigma w_i^2 N_i / \Sigma w_i N_i$$

w_i is the molecular weight averaged over the number of particles, and N_i is the number of particles of chain length i (Mark and Raff, "Higher Polymeric Reactions," New York, 1941).

Course of Polymerisation.—The polymerisation of methyl methacrylate may be explained by a chain mechanism (Mark, "Physical Chemistry of Higher Polymeric Systems", New York, 1940, 309). The methyl methacrylate molecule is thought to become activated, by heat, light, or catalyst, and in this condition it accumulates other methyl methacrylate molecules to form a long chain. Eventually the macro-molecule becomes deactivated by the saturation of the free valencies at the growing ends.

Alyea, Gartland, and Graham (*Ind. Eng. Chem.*, 1942, **34**, 458) have shown that benzoyl peroxide initiates these reaction chains, whereas quinol breaks the chains, and in doing so becomes oxidised to benzoquinone. Strain (*Ind. Eng. Chem.*, 1938, **30**, 345) has examined the polymerisation of methyl methacrylate in various organic solvents, using varying quantities of benzoyl peroxide as catalyst.

If the polymerisation is straightforward, χ_s and t will show a hyperbolic relationship (as Farquharson found to be the case with 2:3-dimethylbutadiene) and the curve for θ_p and t should also be a hyperbola. This was found to hold true in the present case (see Fig.). These results are consistent with Strain's hyperbolic percentage polymer yield-rate curves for 20% solutions of methyl methacrylate in benzene, acetone, and other solvents.

The figure also shows the linear relationships between $M_w/w_m (= n_a\theta_p)$ and n_a , and between $\chi_m/w_m (= n_a\chi_s)$ and n , in accordance with equations (3) and (4).

EXPERIMENTAL.

Measurement of Magneto-optic Rotations.—The apparatus used in these measurements has been described by Anderson, Bedwell, and Le Fèvre (this vol., p. 457). Methyl methacrylate was polymerised at 80° in the presence of a catalyst (1 mole of benzoyl peroxide to 500 moles of monomer). Samples were withdrawn at intervals, and the magneto-optic rotation measured at 20°. For the final determination, a 20% solution in methylene chloride was used. The results are shown in the figure and in Table I; t is the polymerisation time; w_1 is the weight fraction of the solute in the solution; d_{12} and α_{12} are the respective relative density and observed rotation of pure solute or solution.

By the additivity rule, $\theta_1 = (\theta_{12} - \theta_2)/w_1 + \theta_2$, where θ_1 , θ_2 , θ_{12} are the specific rotations of solute, solvent, and solution, respectively.

TABLE I.

t (mins.).	$100w_1$.	$(d_{12})_{20}^{20}$.	α_{12} .	α_{12}/α .	α_1/α .	θ_1 .
Water.						
0	0	0.99820	8.80	—	—	—
Methylene chloride.						
0	0	1.33898	10.80	1.228	1.228	0.919
Methyl methacrylate.						
0	100	0.96698	9.32	1.057	1.057	1.093
15	100	0.97641	9.24	1.050	1.050	1.076
30	100	0.98502	9.16	1.042	1.042	1.056
45	100	0.99773	9.04	1.030	1.030	1.032
60	100	1.00788	8.96	1.018	1.018	1.012
75	100	1.01619	8.88	1.008	1.008	0.992
180	20.04	1.31487 *	10.72	1.227	1.173	0.989

* $(d_1)_{20}^{20} = 1.18630$.

Measurement of Magnetic Susceptibility.—Measurements were made at 20°, using the Gouy apparatus described by Anderson, Bedwell, and Le Fèvre (*loc. cit.*). The process of polymerisation was catalysed by benzoyl peroxide at 80°, as described in the previous section. Samples were withdrawn at intervals for measurement. The final polymer was measured both in 18% solution and in the finely powdered state. The results are shown in the figure and in Table II; t is the polymerisation time, and χ_s is the specific susceptibility of the polymerising substance.

TABLE II.

t (mins.)	0	15	30	45	60	66	75	180
χ_s	0.5370	0.5511	0.5670	0.5776	0.5809	0.5860	0.5881	0.5909 *
								0.5909 *

* Measurements on powder and solution respectively.

Purification of Methyl Methacrylate.—The methyl methacrylate was as supplied by I.C.I. Ltd. stabilised with quinol (0.5%). It was fractionally distilled under reduced pressure and the fraction retained (n_D^{20} 1.4143) was frozen at -70°, redistilled under high vacuum (after Walling and Briggs), and stored at -70° in the dark, with the addition of quinol as stabiliser, in the proportion of 1 mole of quinol to 4000 moles of methyl methacrylate.

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ROYAL AIRCRAFT ESTABLISHMENT,
FARNBOROUGH, HANTS.

[Received, December 14th, 1946.]

251. Synthetic Antimalarials. Part XXI. 4-Arylamino-6-aminoalkylaminopyrimidines. Further Variations.

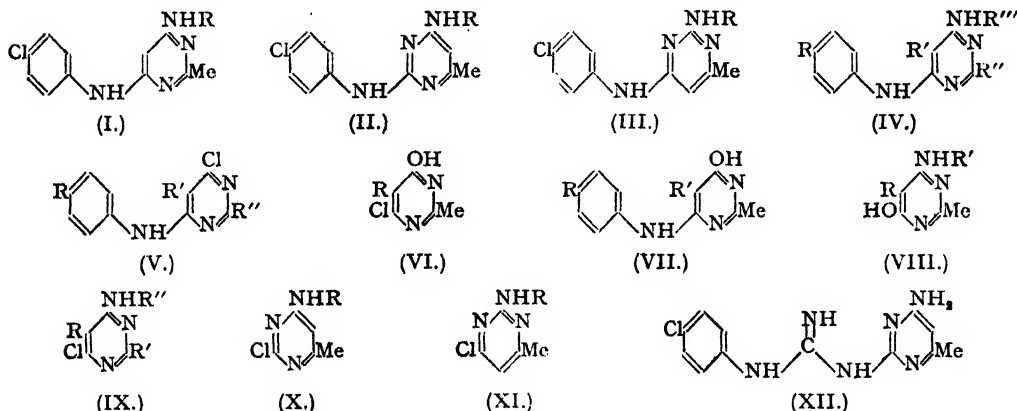
By F. R. BASFORD, F. H. S. CURD, E. HOGGARTH, and F. L. ROSE.

An alternative method of synthesis has been devised for the inactive 4-arylamino-6-aminoalkylamino-2-methylpyrimidines (type I) described in Part VIII (*J.*, 1946, 713), and, employing both this and the original route, substituents such as methyl, ethyl, and phenyl have been introduced into position 5 of the pyrimidine nucleus. These new derivatives were inactive, as were also related compounds in which the 2-methyl group was replaced by amino.

The importance of the aminoalkylamino-side chain in the active 2-arylamino-4-aminoalkylamino- and 4-arylamino-2-aminoalkylamino-6-methylpyrimidines described earlier in this series (*J.*, 1946, 345, 351, 366, 370, 378) has been shown by the lack of activity in compounds, now synthesised, in which that grouping is replaced by primary amino.

Differences in chemical reactivity of several related chloropyrimidine derivatives are discussed.

CHRONOLOGICALLY the work described in this paper follows that reported in Part VIII (*J.*, 1946, 713) which concerned the synthesis of a variety of 4-arylamino-6-aminoalkylamino-2-methylpyrimidines including compounds of type (I; R = dialkylaminoalkyl). All these compounds were found to be without activity against *P. gallinaceum* in chicks. In the same paper we drew attention to the fact that in compounds of type (I) there do not exist two amidine units capable of independent tautomerism as are found in the two isomeric types (II) and (III).



Since one important development of our work (see Part X, *J.*, 1946, 729) was in part based on the recognition of the possible significance of this difference, it seemed desirable to demonstrate with as much certainty as possible that antimalarial activity could not be developed in compounds of type (I). Thus, for example, in a series of simple 2-amino-4-aminoalkylaminopyrimidines, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 357) have shown that the introduction of a substituent into position 5 of the pyrimidine nucleus induced antimalarial activity. Clearly, this was a device that needed to be tried in the present instance, although it was appreciated that the two cases might not be comparable since it had been suggested (*idem, ibid.*) that the activity of the simple pyrimidines might be associated with an interference with nucleoside synthesis and the 5-substituent gave a closer structural resemblance to the purines, whereas we in the past have stressed the relationship of the anilino-pyrimidines to riboflavin. The new preparations were of type (IV; R' = Me, Et, or Ph; R'' = Me). Not all of these were made by the general method described in the earlier paper, namely through the reaction of an aminoalkylamine with the appropriately substituted 4-chloro-6-arylamino-2-methylpyrimidine (V; R'' = Me), itself obtained either directly by condensing a 4:6-dichloro-2-methylpyrimidine with an arylamine, or indirectly from a 4-chloro-6-hydroxy-2-methylpyrimidine (VI) by interaction with an arylamine followed by treatment of the resulting 4-arylamino-6-hydroxy-2-methylpyrimidine (VII) with phosphoryl chloride. A useful alternative method of synthesis has now been developed in which the arylamino- and aminoalkylamino-groups are introduced in the reverse order. The method is best illustrated by its application to the original type (I). β -Diethylaminoethylamine and γ -diethylaminopropylamine when heated with 4-chloro-6-hydroxy-2-methylpyrimidine (VI; R = H) gave respectively

4- β -diethylaminoethylamino- (VIII; $R = H$, $R' = [CH_2]_2 \cdot NEt_2$) and 4- γ -diethylaminopropylamino-6-hydroxy-2-methylpyrimidine (VIII; $R = H$, $R' = [CH_2]_3 \cdot NEt_2$) as their hydrochlorides. Treatment of these hydrochlorides with boiling phosphoryl chloride converted them into 4-chloro-6- β -diethylaminoethylamino- (IX; $R = H$, $R' = Me$, $R'' = [CH_2]_2 \cdot NEt_2$) and 4-chloro-6- γ -diethylaminopropylamino-2-methylpyrimidine (IX; $R = H$, $R' = Me$, $R'' = [CH_2]_3 \cdot NEt_2$) respectively. When a similar series of reactions was tried starting with 8-diethylamino- α -methylbutylamine it was found impossible to crystallise the intermediate 4-8-diethylamino- α -methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride, but treatment of the crude product with phosphoryl chloride gave 4-chloro-6-8-diethylamino- α -methylbutylamino-2-methylpyrimidine (IX; $R = H$, $R' = Me$, $R'' = CHMe \cdot [CH_2]_3 \cdot NEt_2$) in good yield. The above compounds of type (IX) underwent smooth reaction with *p*-chloroaniline in boiling aqueous solution as their monohydrochlorides in presence of a little extra hydrochloric acid, to give the corresponding 4-*p*-chloroanilino-6-dialkylaminoalkylamino-2-methylpyrimidines (I; $R = [CH_2]_2 \cdot NEt_2$, $[CH_2]_3 \cdot NEt_2$, or $CHMe \cdot [CH_2]_3 \cdot NEt_2$) described in Part VIII (*loc. cit.*). In these reactions with *p*-chloroaniline no obvious differences could be detected between the reactivity of the 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines and the isomeric 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (X) (see Part XV, this vol., p. 783) and 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidines (XI) (Part VI, *J.*, 1946, 370). No appreciable condensation occurred, even in the last two instances, when the chloropyrimidines were employed as free bases with addition of a trace of hydrochloric acid. The need for slightly more than one equivalent of acid to facilitate the reaction suggested that the chlorine atom was only labile after salt formation had occurred on the dialkylamino-group of the side chain.

A comparison with the three isomeric types of chlorodialkylaminoalkylaminomethylpyrimidines was provided by the corresponding unsubstituted amino-compounds. Like 2-chloro-4-amino- (X; $R = H$) and 4-chloro-2-amino-6-methylpyrimidine (XI; $R = H$), 4-chloro-6-amino-2-methylpyrimidine (IX; $R = R' = H$, $R' = Me$) reacted readily with *p*-chloroaniline in boiling aqueous solution in presence of only a little hydrochloric acid. The apparent normal reactivity of the 4-chloro-6-amino- and 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines in comparison with their respective isomers was in direct contrast to that of the 4-chloro-6-aryl-amino-2-methylpyrimidines (IX; $R = H$, $R' = Me$, $R'' = aryl$) which were found to be less reactive than the corresponding 2-chloro-4-aryl-amino- (X; $R = aryl$) and 4-chloro-2-aryl-amino-6-methylpyrimidines (XI; $R = aryl$) (see Part VIII, *loc. cit.*). This conforms with the suggestion there advanced that in arylaminopyrimidines there is a strong tendency for the linking nitrogen atom to conjugate with the benzene ring.

Several points may be noted in connection with the synthesis of compounds of type (IV; $R'' = Me$) described in detail in the experimental section. In the preparation of 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine (V; $R = OMe$, $R' = R'' = Me$), required for the synthesis of (IV; $R = OMe$, $R' = R'' = Me$, $R''' = [CH_2]_2 \cdot NEt_2$), by condensation of 4 : 6-dichloro-2 : 5-dimethylpyrimidine with *p*-anisidine in aqueous acetone catalysed by hydrochloric acid, no formation of di-condensation product was observed. Even the use of two molecular proportions of *p*-anisidine gave exclusively 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine in contrast to the formation mainly of 4 : 6-di-*p*-anisidino-2-methylpyrimidine from 4 : 6-dichloro-2-methylpyrimidine and two equivalents of *p*-anisidine under identical conditions (see Part VIII). This steric effect of a 5-substituent was also noticed during the synthesis of 4-*p*-chloroanilino-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (IV; $R = Cl$, $R' = Et$, $R'' = Me$, $R''' = [CH_2]_3 \cdot NEt_2$). Whereas, as noted above, compounds of type (IX; $R' = Me$, $R'' = dialkylaminoalkyl$) containing no substituent in the 5-position ($R = H$) condensed readily on boiling with *p*-chloroaniline in aqueous solution containing a little more than one equivalent of hydrochloric acid, no corresponding condensation occurred between 4-chloro-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (IX; $R = Et$, $R' = Me$, $R'' = [CH_2]_3 \cdot NEt_2$) and *p*-chloroaniline under similar conditions. Higher temperatures were found to be necessary to effect condensation. The steric effect of a 5-phenyl group was even more marked than that of methyl or ethyl. Thus the reaction of *p*-chloroaniline with 4 : 6-dichloro-5-phenyl-2-methylpyrimidine to give 4-chloro-6-*p*-chloroanilino-5-phenyl-2-methylpyrimidine (V; $R = Cl$, $R' = Ph$, $R'' = Me$) failed completely in boiling aqueous acetone with added hydrochloric acid, gave small yields in boiling alcohol, but succeeded at 115–120° in an equivalent of acetic acid. Tests using *P. gallinaceum* in chicks, carried out by our colleague, Dr. D. G. Davey, with the compounds of type (IV; $R'' = Me$), showed that the introduction of a substituent into the 5-position of type (I) failed to confer antimalarial activity.

The necessity for the aminoalkyl group (R) in types (II) and (III) to promote antimalarial

activity was shown by the inactivity in the same test of 4-amino-2-*p*-chloroanilino- (II; R = H) and 2-amino-4-*p*-chloroanilino-6-methylpyrimidine (III; R = H). The former was made by condensing (X; R = H) with *p*-chloroaniline, as mentioned above, and also by the action of ammonia on 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine at 140–150°. When, however, the action of ammonia on 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine was tried with a view to the preparation of (XII), in order to assess the need for the aminoalkyl group in the active 2-*p*-chlorophenylguanidino-4-aminoalkylamino-6-methylpyrimidines described in Part IV (J., 1946, 362), it was found that 2-amino-4-*p*-chloroanilino-6-methylpyrimidine was the main product. Hydrolysis of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine with *N*-hydrochloric acid has been shown by Spinks and Tottey (*Ann. Trop. Med. Parasit.*, 1945, 39, 190) to give *p*-chloroaniline, 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine, ammonia, and carbon dioxide. Analogously, it is suggested that 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine by ammonolysis gave *p*-chloroaniline and 4-chloro-2-amino-6-methylpyrimidine which then interacted to yield (III; R = H).

As a further extension of the investigation of compounds of type (IV) it seemed desirable to study compounds containing an amino-group in the 2-position (R' = NH₂). The presence of such a group, in association with the anilino-residue, would provide the two linked independent amidine units which are a feature of types (II) and (III) without reference to the aminoalkyl-amino-group, and the only function required of the latter would be that of conditioning the pharmacology of the drug molecule.

Like 4 : 6-dichloro-2-methylpyrimidine, 4 : 6-dichloro-2-aminopyrimidine reacted with *p*-chloroaniline in boiling aqueous acetone in presence of a little hydrochloric acid as catalyst to give 4-chloro-2-amino-6-*p*-chloroanilinopyrimidine (V; R = Cl, R' = H, R'' = NH₂). This condensed smoothly with dialkylaminoalkylamines at 150–160°. In this way the following were prepared: 2-amino-4-*p*-chloroanilino-6-β-diethylaminoethylamino- (IV; R = Cl, R' = H, R'' = NH₂, R''' = [CH₂]₂·NEt₂) and 2-amino-4-*p*-chloroanilino-6-γ-diethylaminopropylaminopyrimidine (IV; R = Cl, R' = H, R'' = NH₂, R''' = [CH₂]₃·NEt₂) and the corresponding compounds containing the β-dimethylaminoethylamino-, γ-dimethylaminopropylamino-, and δ-diethylamino-α-methylbutylamino- side chains. 2-Amino-4-*p*-chloroanilino-6-β-diethylaminoethylaminopyrimidine was also obtained by reaction of *p*-chloroaniline hydrochloride with 4-chloro-2-amino-6-β-diethylaminoethylaminopyrimidine (IX; R = H, R' = NH₂, R'' = [CH₂]₂·NEt₂) which resulted from condensation of β-diethylaminoethylamine with 4 : 6-dichloro-2-aminopyrimidine. The former method of synthesis was also employed for the preparation of 2-amino-4-*p*-anisidino- (IV; R = OMe, R' = H, R'' = NH₂, R''' = [CH₂]₂·NEt₂) and 2-amino-4-*p*-toluidino-6-β-diethylaminoethylaminopyrimidine (IV; R = Me, R' = H, R'' = NH₂, R''' = [CH₂]₂·NEt₂).

None of these compounds containing an amino-group in the 2-position of the pyrimidine nucleus exhibited any antimalarial activity, nor did any of the several 5-ethyl or 5-phenyl derivatives which were prepared (*vide infra*). Similar lack of activity characterised a series of 4-chloro-2-amino-6-aminokylamino-5-ethyl- and -phenyl-pyrimidines which thus resemble the related 4-chloro-2-amino-6-dialkylaminoalkylamino-5-methylpyrimidines investigated by Hull, Lovell, Openshaw, and Todd (Part XI, this vol., p. 41).

EXPERIMENTAL.

4-β-Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R' = [CH₂]₂·NEt₂).—4-Chloro-6-hydroxy-2-methylpyrimidine (14.4 g.) (Part VIII, *loc. cit.*) and β-diethylaminoethylamine (11.6 g.) were heated at 150–160° for 8 hours to give 4-β-diethylaminoethylamino-6-hydroxy-2-methylpyrimidine hydrochloride which separated from moist alcohol-ethyl acetate as a hydrate which did not lose water on drying at 100°; colourless laminae, m. p. 193–195° (Found : C, 47.9; H, 7.9; N, 20.7; Cl, 13.0. C₁₁H₂₀ON₄·HCl·H₂O requires C, 47.4; H, 7.5; N, 20.1; Cl, 12.8%).

4-γ-Diethylaminopropylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R' = [CH₂]₃·NEt₂).—By substituting γ-diethylaminopropylamine for the β-diethylaminoethylamine in the above preparation this was obtained as its monohydrochloride which crystallised from alcohol-ethyl acetate as colourless needles, m. p. 87–89° (after drying in air at room temperature) [Found : loss on drying at 100°, 6.4, 6.7. C₁₅H₂₄ON₄·HCl·1.5H₂O requires loss (for 1 H₂O), 6.0%] or 186–188° (after drying at 100°) (Found : C, 51.2; H, 8.4; N, 19.7; Cl, 12.3. C₁₅H₂₄ON₄·HCl·0.5H₂O requires C, 50.8; H, 8.5; N, 19.75; Cl, 12.5%).

4-Chloro-6-β-diethylaminoethylamino-2-methylpyrimidine (IX; R = H, R' = Me, R'' = [CH₂]₂·NEt₂).—4-β-Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine hydrochloride (20 g.) and phosphoryl chloride (75 c.c.) were boiled under reflux for 3 hours. After removal of most of the excess of phosphoryl chloride under reduced pressure, the residue was poured on ice, and the solution made strongly alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the combined acetic acid extracts were treated with sodium hydroxide and shaken with chloroform. Evaporation of the dried (K₂CO₃) extract gave the chloropyrimidine as

a colourless oil (yield, 9.9 g.), b. p. 136—137°/0.15 mm. (Found: C, 54.0; H, 7.8. $C_{11}H_{19}N_4Cl$ requires C, 54.4; H, 7.8%). It gave a *dipicrate* which crystallised from methanol as yellow laminae, m. p. 144—145° (Found: C, 39.7; H, 3.8; N, 20.1. $C_{11}H_{19}N_4Cl \cdot 2C_6H_3O_7N_3$ requires C, 39.4; H, 3.6; N, 20.0%).

4-Chloro-6- γ -diethylaminopropylamino-2-methylpyrimidine (IX; R = H, R' = Me, R'' = $[CH_2]_3 \cdot N \cdot Et_2$), prepared similarly from 4- γ -diethylaminopropylamino-6-hydroxy-2-methylpyrimidine hydrochloride (dried at 100°) (17.5 g.) and phosphoryl chloride (75 c.c.), was obtained as a colourless oil (yield, 8.7 g.), b. p. 143—145°/0.15 mm. (Found: C, 55.9; H, 8.1; N, 21.7; Cl, 13.4. $C_{12}H_{21}N_4Cl$ requires C 56.1; H, 8.2; N, 21.8; Cl, 13.8%). The *dipicrate* crystallised from methanol in yellow laminae, m. p. 158—159° (Found: C, 40.2; H, 3.6; N, 19.8. $C_{12}H_{21}N_4Cl \cdot 2C_6H_3O_7N_3$ requires C 40.3; H, 3.8; N, 19.6%).

Condensation of 4-Chloro-6- β -diethylaminoethylamino-2-methylpyrimidine with p-Chloroaniline.—A mixture of (IX; R = H, R' = Me, R'' = $[CH_2]_3 \cdot N \cdot Et_2$) (4.85 g.), *p*-chloroaniline (2.55 g.), water (25 c.c.), and 10*N*-hydrochloric acid (2.2 c.c.) was refluxed for 6 hours. The cooled solution was treated with sodium hydroxide; the product then separated as an oil which soon solidified. The solid was collected and dissolved in 5% acetic acid, and the solution was treated with decolourising carbon and filtered. The product was then reprecipitated by the addition of sodium hydroxide, filtered off, dried, and crystallised from light petroleum (b. p. >120°) (yield, 86.2%); it had m. p. 148° undepressed on admixture with 4-*p*-chloroanilino-6- β -diethylaminoethylamino-2-methylpyrimidine (see Part VIII) (Found: C, 61.1; H, 7.0; N, 21.2; Cl, 10.3. Calc. for $C_{17}H_{24}N_6Cl$: C, 61.3; H, 7.2; N, 21.0; Cl, 10.5%).

Condensation of 4-Chloro-6- γ -diethylaminopropylamino-2-methylpyrimidine with p-Chloroaniline.—4-Chloro-6- γ -diethylaminopropylamino-2-methylpyrimidine (5.1 g.), *p*-chloroaniline (2.55 g.), water (25 c.c.), and 10*N*-hydrochloric acid (2.2 c.c.) were boiled under reflux for 2 hours, and the solution was cooled and made alkaline with sodium hydroxide. The precipitated oil, isolated with chloroform, was extracted with 5% acetic acid. Basification (with sodium hydroxide) of the clarified acetic acid solution and extraction with chloroform followed by evaporation of the dried solution gave the base which crystallised from light petroleum (b. p. >120°); it had m. p. 129—131° identical with 4-*p*-chloroanilino-6- γ -diethylaminopropylamino-2-methylpyrimidine made by the method of Part VIII (Found: C, 62.1; H, 7.5; N, 19.9. Calc. for $C_{18}H_{26}N_6Cl$: C, 62.2; H, 7.5; N, 20.1%).

4-Chloro-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine (IX; R = H, R' = Me, R'' = $CHMe \cdot [CH_2]_3 \cdot N \cdot Et_2$).—4-Chloro-6-hydroxy-2-methylpyrimidine (28.9 g.) and δ -diethylamino- α -methylbutylamine (31.6 g.) were mixed and heated at 150—160° for 8 hours. To the cooled residue phosphoryl chloride (180 c.c.) was added, the mixture refluxed for 3 hours, excess of phosphoryl chloride removed under reduced pressure, and the residue poured on ice. The resulting solution was made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) chloroform solution and distillation of the residual oil gave the *chloropyrimidine* (yield, 36.4 g.), b. p. 168—170°/0.125 mm. (Found: C, 59.2; H, 8.3; N, 19.5; Cl, 12.7. $C_{14}H_{22}N_4Cl$ requires C, 59.0; H, 8.8; N, 19.7; Cl, 12.5%). The *dipicrate* crystallised from alcohol-2-ethoxyethanol in small yellow laminae, m. p. 171—173° (Found: C, 41.7; H, 4.2; N, 19.1. $C_{14}H_{22}N_4Cl \cdot 2C_6H_3O_7N_3$ requires C, 42.0; H, 4.2; N, 18.9%).

Condensation of 4-Chloro-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine with p-Chloroaniline.—4-Chloro-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine (5.7 g.), *p*-chloroaniline (2.55 g.), water (25 c.c.), and 10*N*-hydrochloric acid (2.2 c.c.) were refluxed for 2 hours, and the resulting solution was cooled and made alkaline with sodium hydroxide. The precipitated oil was collected and extracted with 5% acetic acid, and the acetic acid extract clarified with carbon, filtered, and added to excess of sodium hydroxide solution. The oily product was extracted with chloroform, and the solution dried and evaporated. Distillation of the residue gave 4-*p*-chloroanilino-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine, b. p. 220—225°/0.15 mm., identified as its *dipicrate*, m. p. 159—161° (Found: C, 46.2; H, 4.3; N, 18.2. $C_{20}H_{30}N_6Cl \cdot 2C_6H_3O_7N_3$ requires C, 46.1; H, 4.3; N, 18.5%). In Part VIII (*loc. cit.*) the m. p. of this picrate is given as 149—151°. The discrepancy is thought to be due to dimorphism, since repeat preparations of this picrate sometimes gave m. p. 149—151°, sometimes 159—161°, and sometimes intermediately. The exact conditions of crystallisation to obtain the two forms were not fully elucidated, but a preparation of the picrate from base made according to the method of Part VIII which had m. p. 159—161° (Found: C, 45.9; H, 4.3; N, 18.6%) showed no depression with the picrate described above.

4-Amino-2-*p*-chloroanilino-6-methylpyrimidine (II; R = H).—(a) 2-Chloro-4-amino-6-methylpyrimidine (7.2 g.), *p*-chloroaniline (6.4 g.), water (25 c.c.), and 10*N*-hydrochloric acid (0.5 c.c.) were refluxed for 1 hour. A clear solution was obtained after a few minutes refluxing, and the product then gradually separated. The mixture was diluted with water and made alkaline with ammonia, and the solid collected. The solid was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was extracted with chloroform, and the solution dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene-light petroleum gave colourless needles, m. p. 121—123°.

(b) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (10 g.) and aqueous ammonia (30 c.c.) were heated in a sealed tube at 140—150° for 12 hours. The contents of the tube were diluted with water and extracted with chloroform. Evaporation of the dried chloroform extract gave an oil which was purified by vacuum distillation (b. p. 190—192°/0.5 mm.). Crystallisation from benzene-light petroleum gave 4-amino-2-*p*-chloroanilino-6-methylpyrimidine, m. p. 121—122° undepressed in admixture with material made by method (a) (Found: C, 56.7; H, 4.5; Cl, 15.1. $C_{11}H_{11}N_4Cl$ requires C, 56.3; H, 4.7; Cl, 15.1%) (4394).

2-Amino-4-*p*-chloroanilino-6-methylpyrimidine (III; R = H).—4-Chloro-2-amino-6-methylpyrimidine (7.2 g.), *p*-chloroaniline (6.4 g.), water (25 c.c.), and 10*N*-hydrochloric acid (0.5 c.c.) were refluxed for 1 hour. The reaction mixture was cooled, diluted with water, and made alkaline with ammonia. The precipitated product was filtered off, washed with water, and crystallised from aqueous alcohol, giving 2-amino-4-*p*-chloroanilino-6-methylpyrimidine as colourless needles, m. p. 216—218° (Found: Cl, 15.2. $C_{11}H_{11}N_4Cl$ requires Cl, 15.1%) (4618).

Reaction of 4-Chloro-2-p-chlorophenylguanidino-6-methylpyrimidine with Ammonia (Experiment by Dr. P. A. Barrett).—4-Chloro-2-p-chlorophenylguanidino-6-methylpyrimidine (5 g.) and saturated alcoholic ammonia (25 c.c.) were heated in a sealed tube at 175° for 12 hours. The contents of the tube were evaporated to dryness and the residue was stirred with water. The resulting solid on fractional crystallisation from dilute alcohol gave 2-amino-4-p-chloroanilino-6-methylpyrimidine, m. p. and mixed m. p. 216–218° (Found: C, 56.2; H, 4.4; N, 23.7; Cl, 15.4. Calc. for $C_{11}H_{11}N_4Cl$: C, 56.3; H, 4.7; N, 23.9; Cl, 15.1%), as the less soluble fraction and p-chloroaniline as the more soluble.

4-Amino-6-p-chloroanilino-2-methylpyrimidine (I; R = H).—4-Chloro-6-amino-2-methylpyrimidine (7.2 g.), p-chloroaniline (6.4 g.), water (25 c.c.), and 10N-hydrochloric acid (0.5 c.c.) were refluxed for 1 hour. The reaction mixture was diluted with water and made alkaline with ammonia, and the product filtered off. The product was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was filtered off and crystallised from aqueous alcohol, giving the pyrimidine as colourless flat prisms, m. p. 192–194° (Found: C, 56.4; H, 4.6; Cl, 15.2. $C_{11}H_{11}N_4Cl$ requires C, 56.3; H, 4.7; Cl, 15.1%).

4-Chloro-6-p-chloroanilino-2:5-dimethylpyrimidine (V; R = Cl, R' = R'' = Me).—(a) 4:6-Dichloro-2:5-dimethylpyrimidine (8.85 g.) (Huber and Holscher, *Ber.*, 1938, 71, 87), p-chloroaniline (6.4 g.), water (40 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (2 c.c.) were refluxed for 2 hours. The resulting solution was diluted with water and ammonia added to give an alkaline reaction to Brilliant-yellow. The precipitated base was filtered off, dissolved in alcohol with the addition of a little ammonia, and poured into water. The solid was collected, washed with water, dried, and crystallised from alcohol, giving colourless thick prisms (9 g.), m. p. 176–177° (Found: C, 54.1; H, 3.9; N, 16.2; Cl, 26.2. $C_{12}H_{11}N_4Cl_2$ requires C, 53.7; H, 4.1; N, 15.7; Cl, 26.5%).

(b) 4:6-Dichloro-2:5-dimethylpyrimidine (5.3 g.) and p-chloroaniline (4.2 g.) were heated in acetic acid (30 c.c.), containing a crystal of potassium iodide, at 40° for 20 hours. Addition of sodium acetate (4 g.) and dilution with water gave 4-chloro-6-p-chloroanilino-2:5-dimethylpyrimidine which was filtered off, washed with water, and dried. It had m. p. and mixed m. p. 176° after crystallisation from benzene-light petroleum (Found: Cl, 26.5%).

4-Chloro-6-hydroxy-2:5-dimethylpyrimidine (VI; R = Me).—4:6-Dichloro-2:5-dimethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled together under reflux for 1 hour (complete homogeneity was obtained after $\frac{1}{2}$ hour). The solution was cooled, made alkaline with sodium hydroxide, and then acidified with acetic acid. The precipitated product was filtered off and purified by dissolution in ammonia and reprecipitation with acetic acid. After drying, it crystallised from alcohol in colourless slender prisms (yield 16.3 g.), m. p. 225° (Found: C, 45.5; H, 4.4; N, 17.5; Cl, 22.8. $C_8H_8ON_4Cl$ requires C, 45.4; H, 4.4; N, 17.7; Cl, 22.4%).

4-Chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (IX; R = R' = Me, R'' = $[CH_2]_2 \cdot NEt_2$).—4-Chloro-6-hydroxy-2:5-dimethylpyrimidine (25 g.) and β -diethylaminoethylamine (18.3 g.) were mixed and heated at 150–160° for 8 hours. A portion of the resulting solid, on treatment with excess of picric acid in methanol solution, gave 4- β -diethylaminoethylamino-6-hydroxy-2:5-dimethylpyrimidine *dipicrate* which crystallised from alcohol in yellow rectangular prisms, m. p. 154° (Found: C, 41.6; H, 4.2; N, 20.2. $C_{15}H_{22}ON_4 \cdot 2C_6H_3O_7N_3$ requires C, 41.4; H, 4.0; N, 20.1%). The remainder of the hydrochloride was refluxed with phosphoryl chloride (220 c.c.) for 5 hours and the excess of phosphoryl chloride then removed by distillation under reduced pressure and the residue poured on ice. Addition of sodium hydroxide to the solution liberated the chloro-compound which was extracted with chloroform, and the extract was dried and evaporated. The residue was distilled in a vacuum giving 4-chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (21.9 g.), b. p. 139°/0.085 mm. (Found: C, 56.1; H, 8.2; Cl, 13.5. $C_{12}H_{17}N_4Cl$ requires C, 56.1; H, 8.2; Cl, 13.8%). It formed a *hydrate* which crystallised from light petroleum (b. p. 60–80°) in colourless thick laminae, m. p. 80° (Found: C, 52.6; H, 8.4; N, 20.3. $C_{12}H_{17}N_4Cl \cdot H_2O$ requires C, 52.5; H, 8.4; N, 20.4%), and a *dipicrate* which separated from alcohol in yellow laminae, m. p. 143° (Found: N, 19.5. $C_{12}H_{17}N_4Cl \cdot 2C_6H_3O_7N_3$ requires N, 19.6%).

4- δ -Diethylamino- α -methylbutylamino-6-hydroxy-2:5-dimethylpyrimidine (VIII; R = Me, R' = CHMe $[CH_2]_3 \cdot NEt_2$).—4-Chloro-6-hydroxy-2:5-dimethylpyrimidine (31.7 g.) and δ -diethylamino- α -methylbutylamine (31.6 g.) were mixed and heated at 150–160° for 8 hours with stirring to give, on cooling, a viscous mass of 4- δ -diethylamino- α -methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride which could not be crystallised. The *dipicrate*, prepared from the hydrochloride with excess of picric acid in methanol, crystallised from alcohol; m. p. 163–164° (Found: C, 43.9; H, 4.8. $C_{18}H_{28}ON_4 \cdot 2C_6H_3O_7N_3$ requires C, 43.9; H, 4.6%).

4-Chloro-6- δ -diethylamino- α -methylbutylamino-2:5-dimethylpyrimidine (IX; R = R' = Me, R'' = CHMe $[CH_2]_3 \cdot NEt_2$).—Phosphoryl chloride (225 c.c.) was added to the above crude hydrochloride (62 g.) and the mixture boiled under reflux for 4 hours. Most of the excess of phosphoryl chloride was removed under diminished pressure, the residue poured on ice, and, after solution had occurred, sodium hydroxide added to alkalinity, the oily product extracted with chloroform, and the extract dried and evaporated. Distillation of the residue gave the *chloropyrimidine* as a colourless oil (yield, 22.05 g.), b. p. 144–145°/0.055 mm. (Found: Cl, 12.1, 12.3. $C_{15}H_{21}N_4Cl$ requires Cl, 11.9%). A crystalline derivative was not obtained.

4-p-Chloroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (IV; R = Cl, R' = R'' = Me, R''' = $[CH_2]_2 \cdot NEt_2$).—(a) 4-Chloro-6-p-chloroanilino-2:5-dimethylpyrimidine (14.6 g.), β -diethylaminoethylamine (15 g.), and a crystal of potassium iodide were heated at 150–160° for 6 hours with stirring. The resulting melt was dissolved in dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. After removal of the solvent the residue was stirred with 5% acetic acid, and the extract separated, stirred with decolourising carbon, and filtered. The filtrate was then made strongly alkaline with sodium hydroxide and extracted with chloroform, and the extract dried and evaporated. Distillation of the residual oil afforded 4-p-chloroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine as a colourless oil (yield, 11.6 g.), b. p. 200°/0.07 mm. (Found: C, 61.6; H, 7.5; N, 19.7; Cl, 10.2. $C_{15}H_{18}N_4Cl$ required C, 62.2; H, 7.5; N, 20.1; Cl, 10.2%). The base was converted into its *dihydrochloride* by dissolving in 2N-hydrochloric acid and

evaporating the solution to dryness. The residue was dried and freed from adhering hydrochloric acid by dissolving in alcohol and evaporation to dryness under reduced pressure several times. Crystallisation from alcohol-ethyl acetate then gave thin colourless prisms, m. p. 263–264° (Found: C, 51.0; H, 6.4; N, 16.4; Cl, 16.2. $C_{18}H_{22}N_6Cl_2 \cdot 2HCl$ requires C, 51.4; H, 6.7; N, 16.65; Cl, 16.9%) (3990).

(b) A mixture of 4-chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (5.13 g.), *p*-chloroaniline hydrochloride (3.28 g.), and hydrochloric acid (0.25 c.c.) was heated at 150–160° for 6 hours. By direct crystallisation of the resulting solid melt from alcohol-ethyl acetate, 4-*p*-chloroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine dihydrochloride was obtained (yield, 5.7 g.), m. p. and mixed m. p. 262–264° (Found: C, 51.2; H, 6.1; N, 16.4; Cl, 16.5%).

4-*p*-Chloroanilino-6- γ -diethylaminopropylamino-2:5-dimethylpyrimidine (IV; R = Cl, R' = R'' = Me, R''' = $[CH_2]_3 \cdot NEt_3$), prepared by method (a) above from 4-chloro-6-*p*-chloroanilino-2:5-dimethylpyrimidine and γ -diethylaminopropylamine, formed a colourless viscous oil, b. p. 204°/0.045 mm. (Found: C, 62.9; H, 7.8; N, 18.8; Cl, 9.8. $C_{18}H_{22}N_6Cl$ requires C, 63.1; H, 7.7; N, 19.4; Cl, 9.8%) which gave a dihydrochloride as colourless prisms from alcohol-ethyl acetate, m. p. 217–218° (Found: C, 48.8; H, 7.1; N, 14.9; Cl, 15.1. $C_{18}H_{22}N_6Cl_2 \cdot 2H_2O$ requires C, 48.5; H, 7.2; N, 14.9; Cl, 15.1%) (5507).

4-*p*-Chloroanilino-6- γ -dimethylaminopropylamino-2:5-dimethylpyrimidine (IV; R = Cl, R' = R'' = Me, R''' = $[CH_2]_3 \cdot NMe_2$), prepared in a corresponding manner using γ -dimethylaminopropylamine, was obtained as colourless prisms from light petroleum (b. p. 60–80°), m. p. 105° (Found: C, 61.2; H, 7.0; N, 20.6. $C_{17}H_{20}N_6Cl$ requires C, 61.2; H, 7.2; N, 21.0%). It gave a dihydrochloride which crystallised from alcohol-ethyl acetate in tiny colourless prisms, m. p. 275–276° (decomp.) (the m. p. varied slightly with the rate of heating) (Found: C, 49.9; H, 6.3; N, 17.3; Cl, 17.2. $C_{17}H_{20}N_6Cl_2 \cdot 2HCl$ requires C, 50.2; H, 6.4; N, 17.2; Cl, 17.5%) (4067).

4-*p*-Chloroanilino-6- δ -diethylamino- α -methylbutylamino-2:5-dimethylpyrimidine (IV; R = Cl, R' = R'' = Me, R''' = CHMe $\cdot[CH_2]_3 \cdot NEt_3$).—The condensate (150–160° for 6 hours) of 4-chloro-6- δ -diethylamino- α -methylbutylamino-2:5-dimethylpyrimidine (14.93 g.) and *p*-chloroaniline (8.2 g.) was dissolved in dilute hydrochloric acid, made alkaline with sodium hydroxide, and then extracted with chloroform. Evaporation of the dried chloroform extract and distillation of the residue gave the base (9.4 g.) as a colourless highly viscous oil, b. p. 208°/0.55 mm. (Found: C, 64.5; H, 7.8; Cl, 9.5. $C_{21}H_{28}N_6Cl$ requires C, 64.7; H, 8.2; Cl, 9.1%) (3988). No solid salt could be isolated.

4-*p*-Bromoanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (IV; R = Br, R' = R'' = Me, R''' = $[CH_2]_2 \cdot NEt_3$).—4-Chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (10.26 g.) was mixed with *p*-bromoaniline hydrochloride (6.9 g.), a few drops of hydrochloric acid were added, and the whole was heated at 150–160° for 6 hours. The melt, originally fluid, was completely solid after 2.5 hours. Crystallisation from alcohol-ethyl acetate gave the dihydrochloride as colourless thick prisms, m. p. 265–266° (Found: C, 46.3; H, 6.4. $C_{18}H_{22}N_6Br_2 \cdot 2HCl$ requires C, 46.45; H, 6.0%).

4-Chloro-6-*p*-anisidino-2:5-dimethylpyrimidine (V; R = Cl, R' = R'' = Me).—(a) 4:6-Dichloro-2:5-dimethylpyrimidine (8.85 g.), *p*-anisidine (6.15 g.), water (40 c.c.), acetone (20 c.c.), and 10*N*-hydrochloric acid (1 c.c.) were refluxed for 3 hours. The mixture was diluted with water and made alkaline with ammonia. The filtered product was dissolved in 2-ethoxyethanol, and the solution made alkaline by the addition of a little ammonia and then poured into water. The precipitated solid was collected, washed with water, and dried. Crystallised from *n*-propanol, the base (9.5 g.) had m. p. 201° (Found: C, 58.8; H, 5.0; N, 15.8; Cl, 13.1. $C_{15}H_{14}ON_3Cl$ requires C, 59.2; H, 5.3; N, 15.9; Cl, 13.5%).

(b) 4:6-Dichloro-2:5-dimethylpyrimidine (5.31 g.), *p*-anisidine (4.5 g.), glacial acetic acid (30 c.c.), and 10*N*-hydrochloric acid (0.2 c.c.) were stirred at 40–45° for 20 hours. Sodium acetate (4 g.) was then added and the solution diluted with water (300 c.c.). On standing, the product gradually separated and was filtered off, washed with water, and dried. Crystallisation from benzene gave 4-chloro-6-*p*-anisidino-2:5-dimethylpyrimidine (6.4 g.) as colourless needles, m. p. and mixed m. p. 201° (Found: Cl, 13.4%).

4-*p*-Anisidino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (IV; R = OMe, R' = R'' = Me, R''' = $[CH_2]_2 \cdot NEt_3$).—The above chloropyrimidine (10 g.), β -diethylaminoethylamine (14 g.), and a crystal of potassium iodide were heated at 150–160° for 6 hours with stirring. The resulting reaction mixture was worked up as described previously for the corresponding *p*-chloroanilino-compound and gave the base (8.9 g.) as a colourless viscous oil, b. p. 203°/0.5 mm. (Found: C, 67.0; H, 9.3; N, 19.8. $C_{19}H_{24}ON_6$ requires C, 66.5; H, 8.5; N, 20.4%). The dihydrochloride crystallised from alcohol-ethyl acetate in clusters of colourless prisms, m. p. 254–255° (Found: C, 52.5; H, 7.7; N, 16.1; Cl, 16.9. $C_{19}H_{24}ON_6 \cdot 2HCl \cdot H_2O$ requires C, 52.5; H, 7.6; N, 16.1; Cl, 16.4%) (3962).

4-Chloro-6-*p*-nitroanilino-2:5-dimethylpyrimidine (V; R = NO₂, R' = R'' = Me).—4:6-Dichloro-2:5-dimethylpyrimidine (5.22 g.), *p*-nitroaniline (4.55 g.), acetic acid (50 c.c.), and a crystal of potassium iodide were heated at 55–60° for 18 hours. Sodium acetate (3 g.) was then added and the solution diluted with water (500 c.c.). The precipitated solid was filtered off, washed with water, and dried. Crystallised from butanol, the base formed yellow prisms (yield, 5.2 g.), m. p. 208–210° (Found: Cl, 12.9; $C_{15}H_{11}O_2N_3Cl$ requires Cl, 12.7%).

4-*p*-Nitroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (IV; R = NO₂, R' = R'' = Me, R''' = $[CH_2]_2 \cdot NEt_3$).—(a) An intimate mixture of 4-chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine (1.0 g.) and *p*-nitroaniline hydrochloride (0.68 g.) was heated at 150–160° for 6 hours with stirring in the initial stages. The cold melt was dissolved in hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was then extracted several times with 5% acetic acid and the combined acetic acid extracts were added to excess of sodium hydroxide. The precipitated oil was taken up in chloroform, and the solution dried and evaporated. Crystallisation of the residue from light petroleum (b. p. 80–100°) gave the base as thick yellow laminae, m. p. 104–106° (Found: C, 60.4; H, 7.3; N, 23.1. $C_{18}H_{22}O_2N_6$ requires C, 60.3; H, 7.3; N, 23.5%).

(b) 4-Chloro-6-*p*-nitroanilino-5:6-dimethylpyrimidine (1.8 g.), β -diethylaminoethylamine (1.8 g.),

and a trace of potassium iodide were heated at 155–165° for 5 hours and the mixture was worked up in the same way as in (a) to give the base (1.8 g.) which was converted into its *dihydrochloride*. This crystallised from alcohol-ethyl acetate in yellowish rectangular prisms, m. p. 254–256° (Found : C, 50.1; H, 6.5; N, 19.4. $C_{11}H_{10}O_2N_2 \cdot 2HCl$ requires C, 50.1; H, 6.5; N, 19.5%) (4188).

4 : 6-Dichloro-2-methyl-5-ethylpyrimidine.—4 : 6-Dihydroxy-2-methyl-5-ethylpyrimidine (30 g.) (Ferris and Ronzio, *J. Amer. Chem. Soc.*, 1940, **62**, 606) and phosphoryl chloride (110 c.c.) were refluxed for 2 hours and the bulk of the excess of phosphoryl chloride was then removed under diminished pressure. The residue was poured on ice (200 g.), the product extracted with benzene, and the solution dried (Na_2SO_4). The benzene was then removed by distillation through a short fractionating column and the residue distilled giving 4 : 6-dichloro-2-methyl-5-ethylpyrimidine as a colourless oil, b. p. 212–214° (Found : Cl, 37.2. $C_7H_8N_2Cl_2$ requires Cl, 37.2%).

4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (VI; R = Et).—4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled under reflux for 2.5 hours. The resulting clear solution was cooled, made alkaline with ammonia, and then acidified with acetic acid. Next day the product was filtered off and purified by dissolution in dilute sodium hydroxide and reprecipitation with acetic acid. The dried base crystallised from alcohol in colourless elongated prisms (yield, 19.2 g.), m. p. 209° (Found : C, 49.0; H, 5.0; N, 16.4. $C_7H_8ON_2Cl$ requires C, 48.7; H, 5.2; N, 16.2%).

4-p-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine (VII; R = Cl, R' = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (8.63 g.), *p*-chloroaniline (9.6 g.), and hydrochloric acid (0.5 c.c.) were mixed and heated at 160–170° for 8 hours. After cooling, the melt was dissolved in warm aqueous sodium hydroxide, and the solution treated with decolorising carbon and filtered. Addition of acetic acid to the filtrate gave the product which was filtered off, digested with aqueous ammonia, collected, and dried. 4-p-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine crystallised from 2-ethoxyethanol in colourless needles (yield, 8.1 g.), m. p. 275° (Found : C, 59.0; H, 5.9; N, 16.1. $C_{13}H_{14}ON_2Cl$ requires C, 59.2; H, 6.1; N, 15.9%).

4-Chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine (V; R = Cl, R' = Et, R'' = Me).—(a) 4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (5.73 g.) and *p*-chloroaniline (4.3 g.) were dissolved in acetic acid (30 c.c.), a crystal of potassium iodide was added, and the solution was stirred at 35–45° for 20 hours. Sodium acetate (3 g.) was then added and the solution drowned into water to precipitate the base which was filtered off, dried, and crystallised, first from benzene-light petroleum (b. p. 60–80°) and then from dilute alcohol; long colourless rectangular prisms, m. p. 166° (Found : C, 55.6; H, 4.4; N, 14.5; Cl, 25.2. $C_{13}H_{13}N_2Cl_2$ requires C, 55.3; H, 4.6; N, 15.0; Cl, 25.2%).

(b) 4-*p*-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine (8.9 g.) and phosphoryl chloride (45 c.c.) were refluxed for 1½ hours, and the clear solution was cooled and poured on ice. After being stirred for ½ hour the solution was made alkaline with sodium hydroxide and the precipitated product filtered off, washed with water, and dried. On boiling it with benzene a small amount of unchanged hydroxy-compound remained undissolved. This was removed by filtration and the benzene evaporated. Crystallisation of the residue from dilute alcohol gave the same compound as in (a), m. p. and mixed m. p. 166° (Found : C, 55.6; H, 4.4; N, 14.8%).

4- γ -Diethylaminopropylamino-6-hydroxy-2-methyl-5-ethylpyrimidine (VIII; R = Et, R' = $[CH_2]_3 \cdot NEt_2$).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (34.5 g.) and γ -diethylaminopropylamine (26 g.) were heated at 150–160° for 8 hours, with stirring until the melt solidified. A small sample of the resulting hydrochloride of 4- γ -diethylaminopropylamino-6-hydroxy-2-methyl-5-ethylpyrimidine on treatment with picric acid in alcohol gave the *dipicrate* which crystallised from 2-ethoxyethanol-alcohol in flat yellow prisms, m. p. 188° (Found : C, 42.9; H, 4.7; N, 19.4. $C_{14}H_{18}ON_4 \cdot 2C_6H_3O_7N_3$ requires C, 43.1; H, 4.4; N, 19.3%).

4-Chloro-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (IX; R = Et, R' = Me, R'' = $[CH_2]_3 \cdot NEt_2$).—The above hydrochloride (59.5 g.) was refluxed with phosphoryl chloride (225 c.c.) during 15 hours, and the reaction mixture worked up as described previously for this type of compound, giving the *chloropyrimidine* as a colourless oil, b. p. 142°/0.095 mm. (Found : N, 19.1; Cl, 12.1. $C_{14}H_{18}N_4Cl$ requires N, 19.7; Cl, 12.5%). It gave a *dipicrate* which crystallised from alcohol in yellow tables, m. p. 147–148° (Found : C, 42.0; H, 4.2; N, 18.8. $C_{14}H_{18}N_4Cl \cdot 2C_6H_3O_7N_3$ requires C, 42.0; H, 4.2; N, 18.85%).

4-*p*-Chloroanilino-6- β -diethylaminoethylamino-2-methyl-5-ethylpyrimidine (IV; R = Cl, R' = Et, R'' = Me, R''' = $[CH_2]_3 \cdot NMe_2$).—4-Chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine (2.0 g.), β -diethylaminoethylamine (2.0 g.), and a crystal of potassium iodide were stirred and heated at 140–150° for 6 hours. The resulting mixture was dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The precipitate was separated by decantation and dissolved in 5% acetic acid, and the solution was filtered. On addition of sodium hydroxide to the filtrate, the base was obtained as an oil which was extracted with benzene, and the extract was dried and evaporated. The residual oily base gave a *dihydrochloride* which crystallised from alcohol-ethyl acetate in colourless thick prisms, m. p. 268–270° (decomp.) (Found : C, 52.3; H, 6.8; N, 16.0; Cl', 16.3. $C_{18}H_{22}N_6Cl_2 \cdot 2HCl$ requires C, 52.5; H, 6.9; N, 16.1; Cl', 16.3%) (4046).

4-*p*-Chloroanilino-6- γ -dimethylaminopropylamino-2-methyl-5-ethylpyrimidine (IV; R = Cl, R' = Et, R'' = Me, R''' = $[CH_2]_3 \cdot NMe_2$).—Obtained similarly from 4-chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine and γ -dimethylaminopropylamine, this gave a *dipicrate* which crystallised from alcohol in thick yellow laminæ, m. p. 171–173° (Found : C, 45.1; H, 4.5. $C_{18}H_{22}N_6Cl_2 \cdot 2C_6H_3O_7N_3$ requires C, 44.7; H, 4.0%), and a *dihydrochloride* which crystallised from alcohol-ethyl acetate in colourless flat prisms, m. p. 278–279° (decomp.) (Found : C, 47.7; H, 7.3; N, 15.1; Cl', 15.3. $C_{18}H_{22}N_6Cl_2 \cdot 2HCl \cdot 2H_2O$ requires C, 47.3; H, 7.0; N, 15.3; Cl', 15.6%) (4017).

4-*p*-Chloroanilino-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (IV; R = Cl, R' = Et, R'' = Me, R''' = $[CH_2]_3 \cdot NEt_2$).—4-Chloro-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (8.35 g.), *p*-chloroaniline (4.8 g.), and a few drops of hydrochloric acid were heated at 150–160° for 6 hours with stirring. The melt (cooled) was dissolved out with hydrochloric acid and the solution

made alkaline with sodium hydroxide. The liberated oil was extracted with benzene, and the extract dried and evaporated. Distillation of the remaining oil gave 4-*p*-chloroanilino-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine (6.3 g.), b. p. 210°/0.065 mm. (Found: C, 63.5; H, 8.0. $C_{26}H_{30}N_8Cl$ requires C, 63.9; H, 8.0%), which formed a *dihydrochloride*, colourless prisms from alcohol-ethyl acetate, m. p. 162° (Found: C, 50.9; H, 7.1; N, 14.9; Cl, 14.8. $C_{26}H_{30}N_8Cl_2 \cdot 2HCl \cdot H_2O$ requires C, 51.4; H, 7.3; N, 15.0; Cl, 15.2%).

4-*p*-Anisidino-6-hydroxy-2-methyl-5-ethylpyrimidine (VII; R = OMe, R' = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (17.25 g.), *p*-anisidine (12.3 g.), and hydrochloric acid (1 c.c.) were heated at 160–170° for 3 hours. The mixture was dissolved in dilute sodium hydroxide solution, and the solution treated with decolorising carbon and filtered. Acidification of the filtrate with acetic acid gave a product which was freed from a small amount of unchanged 4-chloro-6-hydroxy-2-methyl-5-ethylpyrimidine by stirring with 10% aqueous ammonia for 3 hours and filtering. After being washed with water and dried, the base crystallised from alcohol in colourless thick prisms, m. p. 199–200° (Found: C, 65.0; H, 6.6; N, 16.3. $C_{14}H_{11}O_2N_3$ requires C, 64.9; H, 6.6; N, 16.2%).

4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (V; R = OMe, R' = Et, R'' = Me).—(a) 4:6-Dichloro-2-methyl-5-ethylpyrimidine (5.73 g.) and *p*-anisidine (4.1 g.) were kept in acetic acid (30 c.c.), with the addition of a crystal of potassium iodide, at 40–45° for 20 hours. After addition of sodium acetate (3 g.) the solution was drowned into water (300 c.c.), and the precipitated product filtered off, washed with water, and crystallised from dilute alcohol; colourless elongated prisms, m. p. 157° (Found: C, 60.6; H, 5.7; N, 15.2. $C_{14}H_{11}ON_3Cl$ requires C, 60.5; H, 5.8; N, 15.1%).

(b) 4-*p*-Anisidino-6-hydroxy-2-methyl-5-ethylpyrimidine (11.9 g.) and phosphoryl chloride (60 c.c.) were boiled under reflux for 1½ hours and the clear solution poured on ice. Addition of ammonia precipitated the product which was purified by crystallisation from dilute alcohol. It then had m. p. 157° either alone or in admixture with material made by method (a) (Found: C, 60.1; H, 5.4%).

4-*p*-Anisidino-6- β -diethylaminoethylamino-2-methyl-5-ethylpyrimidine (IV; R = OMe, R' = Et, R'' = Me, R''' = $[CH_2]_2 \cdot NEt_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2.75 g.) and β -diethylaminoethylamine (2.5 g.) were heated at 155–165° for 8 hours and the mixture worked up as in the case of the corresponding *p*-chloroanilino-compound, giving the *dihydrochloride* as colourless laminae from alcohol-ethyl acetate, m. p. 250–251° (decomp.) (Found: C, 55.5; H, 7.5; N, 15.9; Cl, 16.3. $C_{26}H_{31}ON_8 \cdot 2HCl$ requires C, 55.8; H, 7.7; N, 16.3; Cl, 16.5%) (4048).

4-*p*-Anisidino-6- γ -dimethylaminopropylamino-2-methyl-5-ethylpyrimidine (IV; R = OMe, R' = Et, R'' = Me, R''' = $[CH_2]_3 \cdot NMe_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2.75 g.) and γ -dimethylaminopropylamine (2.5 g.) were heated, with the addition of a trace of potassium iodide, at 150–160° for 8 hours with stirring. The melt was dissolved in dilute hydrochloric acid and the solution poured into excess of sodium hydroxide solution. The precipitated product was collected and purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. The base, isolated by extraction with benzene, crystallised from light petroleum (b. p. 80–100°) in colourless needles, m. p. 106–107° (Found: C, 66.2; H, 7.8; N, 20.3. $C_{19}H_{20}ON_3$ requires C, 66.5; H, 8.5; N, 20.4%) (4069).

4:6-Dichloro-5-phenyl-2-methylpyrimidine.—4:6-Dihydroxy-5-phenyl-2-methylpyrimidine (40 g.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and phosphoryl chloride (140 c.c.) were boiled under reflux for 2 hours. The excess of phosphoryl chloride was then removed under reduced pressure and the residue poured on a mixture of ice and water (300 g.). After ¼ hour's stirring, the product which had separated was filtered off, washed acid-free with water, and crystallised from alcohol; colourless plates, m. p. 160° (Found: C, 55.2; H, 3.1; Cl, 29.1. $C_{11}H_8N_2Cl_2$ requires C, 55.2; H, 3.35; Cl, 29.7%) (4070).

4-Chloro-6-*p*-chloroanilino-5-phenyl-2-methylpyrimidine (V; R = Cl, R' = Ph, R'' = Me).—4:6-Dichloro-5-phenyl-2-methylpyrimidine (11.95 g.) and *p*-chloroaniline (6.4 g.) were ground together, acetic acid (3 g.) was added, and the mixture was heated at 110–115° for 1 hour. The cooled melt was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated base was filtered off, washed with water, and dried. Crystallised from light petroleum (b. p. >120°), it formed colourless prisms (9.5 g.), m. p. 155–156° (Found: C, 62.1; H, 4.1; N, 12.8; Cl, 21.2. $C_{17}H_{13}N_3Cl_2$ requires C, 61.8; H, 3.9; N, 12.7; Cl, 21.5%) (4071).

4-*p*-Chloroanilino-6- β -diethylaminoethylamino-5-phenyl-2-methylpyrimidine (IV; R = Cl, R' = Ph, R'' = Me, R''' = $[CH_2]_2 \cdot NEt_2$).—The above chloropyrimidine (12.0 g.), β -diethylaminoethylamine (12.0 g.), and a crystal of potassium iodide were heated at 150–160° for 6 hours with stirring and then worked up to give the pyrimidine which crystallised from light petroleum (b. p. 40–60°) in colourless laminae, m. p. 88–89° (Found: C, 67.0; H, 7.1; N, 17.5. $C_{23}H_{28}N_6Cl$ requires C, 67.4; H, 6.8; N, 17.1%) (4072).

4-*p*-Chloroanilino-6- γ -diethylaminopropylamino-5-phenyl-2-methylpyrimidine (IV; R = Cl, R' = Ph, R'' = Me, R''' = $[CH_2]_3 \cdot NEt_2$).—The above chloropyrimidine (12.0 g.) was prepared in a similar manner using γ -diethylaminopropylamine in place of β -diethylaminoethylamine, crystallised from light petroleum (b. p. 40–60°) in colourless thick rectangular prisms, m. p. 77–78° (Found: C, 67.7; H, 6.8; N, 16.7. $C_{24}H_{30}N_6Cl$ requires C, 68.0; H, 7.1; N, 16.5%). A crystalline dihydrochloride could not be obtained either from this or the preceding compound.

4-Chloro-2-amino-6-*p*-chloroanilino-5-phenylpyrimidine (V; R = Cl, R' = H, R'' = NH_2).—(a) 4:6-Dichloro-2-aminopyrimidine (12.3 g.) and *p*-chloroaniline (9.6 g.) were ground together, acetic acid (9.0 g.) was added, and the mixture was heated to 110°. After a few minutes at this temperature a vigorous reaction occurred, and the reaction mixture which had previously become fluid and homogeneous suddenly set solid. The cooled and ground melt was boiled with alcohol (150 c.c.) containing ammonia for 1½ hours, then diluted with water, and the product collected and dried. Crystallised from ethyl acetate it formed colourless prisms (yield, 11.6 g.), m. p. 242–243° (Found: C, 47.1; H, 3.2; N, 21.9; Cl, 28.1. $C_{16}H_8N_4Cl_2$ requires C, 47.1; H, 3.1; N, 22.0; Cl, 27.7%). Addition of hydrochloric acid to its alcoholic solution gave a *hydrochloride* as colourless needles, m. p. 252–254° (Found: N, 18.2; Cl, 33.6. $C_{16}H_8N_4Cl_2 \cdot HCl \cdot H_2O$ requires N, 18.1; Cl, 34.4%).

(b) 4:6-Dichloro-2-aminopyrimidine (8.2 g.), *p*-chloroaniline (6.3 g.), water (40 c.c.), acetone (10 c.c.),

and 10*N*-hydrochloric acid (0.5 c.c.) were boiled under reflux for 2 hours. After cooling, the product was filtered off, washed with water, and dissolved in boiling 2-ethoxyethanol with the addition of ammonia to give an alkaline reaction. After dilution with water the precipitated product was filtered off, washed with water, dried, and crystallised from ethyl acetate; m. p. 241—242° either alone or admixed with the product from (a) above (yield, 6.5 g.).

4-Chloro-2-amino-6-*p*-anisidinopyrimidine (V; R = OMe, R' = H, R'' = NH₂).—To an intimate mixture of 4 : 6-dichloro-2-aminopyrimidine (12.3 g.) and *p*-anisidine (9.2 g.), acetic acid (4.5 g.) was added and the mixture heated to 110°; a vigorous reaction then took place. After $\frac{1}{2}$ hour at 110°, the melt was cooled, ground, and stirred with dilute ammonia for 2 hours. The resulting base was filtered off, washed with water, and crystallised from alcohol, giving colourless prisms (8.9 g.), m. p. 224—225° (Found: C, 53.1; H, 4.6; N, 22.1. C₁₁H₁₁ON₄Cl requires C, 52.7; H, 4.4; N, 22.35%). The hydrochloride had m. p. 236° (decomp.) (Found: N, 19.3; Cl, 24.1. C₁₁H₁₁ON₄Cl.HCl requires N, 19.5; Cl, 24.7%).

4-Chloro-2-amino-6-*p*-toluidinopyrimidine (V; R = Me, R' = H, R'' = NH₂), prepared similarly using *p*-toluidine in place of *p*-anisidine, crystallised from alcohol in colourless laminae, m. p. 239—241° (Found: C, 56.1; H, 4.7; N, 23.8. C₁₁H₁₁N₄Cl requires C, 56.3; H, 4.7; N, 23.9%). It formed a hydrochloride, m. p. 259—260° (decomp.) (Found: N, 20.3; Cl, 26.4. C₁₁H₁₁N₄Cl.HCl requires N, 20.3; Cl, 26.4%).

2-Amino-4-*p*-chloroanilino-6- β -diethylaminoethylaminopyrimidine (IV; R = Cl, R' = H, R'' = NH₂, R''' = [CH₂]₂.NEt₂).—(a) 4-Chloro-2-amino-6-*p*-chloroanilinopyrimidine hydrochloride (9.7 g.) and β -diethylaminoethylamine (4.84 g.) were heated at 150—160° for 5 hours, and the mixture was cooled and dissolved in water. To the solution sodium hydroxide was added, and the precipitated product was extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the acid extracts were combined, made alkaline with sodium hydroxide, and extracted with chloroform. The dried chloroform solution, on evaporation, gave the base which crystallised from benzene in colourless laminae (8 g.), m. p. 135° (Found: C, 57.4; H, 7.0; N, 24.7. C₁₈H₂₃N₅Cl requires C, 57.4; H, 6.9; N, 25.1%) (3861).

(b) 4-Chloro-2-amino-6- β -diethylaminoethylaminopyrimidine (6.1 g.) (see below) and *p*-chloroaniline hydrochloride (4.1 g.) were mixed and heated in an oil-bath at 170—180° for 6 hours. The resulting melt was dissolved in warm dilute hydrochloric acid and then worked up as in (a) to give 2-amino-4-*p*-chloroanilino-6- β -diethylaminoethylaminopyrimidine, m. p. and mixed m. p. 134—135°.

By method (a) above a number of other 2-amino-4-arylamino-6-dialkylaminoalkylaminopyrimidines were prepared. Details of these are given in Table I.

4-Chloro-2-amino-6-*p*-chloroanilino-5-ethylpyrimidine (V; R = Cl, R' = Et, R'' = NH₂).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (19.2 g.) (v. Merckat, *Ber.*, 1919, 52, 869) and *p*-chloroaniline (12.75 g.) were ground together, acetic acid (6 g.) was added, and the mixture was heated at 100—110° for $\frac{1}{2}$ hour with stirring. A homogeneous melt was obtained which suddenly solidified after about $\frac{1}{2}$ hour. The cooled and ground melt was dissolved in boiling alcohol with the addition of ammonia to give an alkaline reaction, and the solution poured into water. The precipitated product was filtered off and dried. By crystallisation from benzene it was obtained as colourless tables (19.25 g.), m. p. 158—160° (Found: C, 51.2; H, 4.2; N, 19.4. C₁₂H₁₂N₄Cl₂ requires C, 50.9; H, 4.2; N, 19.8%). The hydrochloride crystallised from alcohol containing a little hydrochloric acid in long colourless prisms, m. p. >290° (Found: C, 45.6; H, 4.5; N, 17.6. C₁₂H₁₂N₄Cl₂.HCl requires C, 45.1; H, 4.1; N, 17.5%).

4-Chloro-2-amino-6-*p*-cyanoanilino-5-ethylpyrimidine (V; R = CN, R' = Et, R'' = NH₂).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (12.8 g.) and *p*-cyanoaniline (7.86 g.) were mixed, and acetic acid (4 g.) was added. After being heated for some time at 120° the fluid mixture suddenly solidified. Heating at 120—130° was continued for 1 hour, and the melt then dissolved in 2-ethoxyethanol, ammonia added, and the solution poured into water. The dried precipitated product crystallised from butanol in colourless rhombs (10 g.), m. p. 230—232° (Found: C, 57.0; H, 4.1; N, 25.1. C₁₃H₁₂N₅Cl requires C, 57.0; H, 4.4; N, 25.6%).

4 : 6-Dichloro-2-amino-5-phenylpyrimidine.—Guanidine nitrate (24.4 g.) was added to a hot solution of sodium (9.2 g.) in methanol (250 c.c.) and, after $\frac{1}{2}$ hour's refluxing, ethyl phenylmalonate (47.2 g.) was added. The mixture was boiled under reflux for 3 hours and then allowed to cool. The solid was collected and the filtrate evaporated; the residue and the solid were combined and dissolved in warm water, and the solution was treated with decolourising carbon and filtered. The filtrate was acidified with acetic acid at 80°, and the product collected, washed with water, and dried (25.6 g.). This 2-amino-4 : 6-dihydroxy-5-phenylpyrimidine (20 g.) and phosphoryl chloride (90 c.c.) were boiled under reflux for 3 hours, and the resulting clear solution was poured on ice (600 g.) with stirring. After 2 hours' stirring, ammonia was gradually added until the mixture was neutral. The solid product was filtered off, washed with water, and dried. Purification by vacuum sublimation at 160—170°/14 mm. followed by crystallisation from alcohol, gave 4 : 6-dichloro-2-amino-5-phenylpyrimidine as colourless plates, m. p. 221—222° (Found: C, 50.3; H, 2.9; N, 17.3. C₁₀H₇N₃Cl₂ requires C, 50.0; H, 2.9; N, 17.5%).

4-Chloro-2-amino-6-*p*-chloroanilino-5-phenylpyrimidine (V; R = Cl, R' = Ph, R'' = NH₂).—Acetic acid (3 g.) was added to an intimate mixture of 4 : 6-dichloro-2-amino-5-phenylpyrimidine (12.0 g.) and *p*-chloroaniline (6.45 g.) and the whole heated at 120—130° for 1.5 hours. The mixture gradually melted and then resolidified. After being ground and stirred with dilute ammonia, the solid product was dissolved in 2-ethoxyethanol, ammonia added to alkalinity, and the solution diluted with water. The crystalline pyrimidine which separated on standing was filtered off, dried, and crystallised from butanol; colourless laminae, m. p. 228—229° (Found: C, 58.0; H, 3.6; N, 16.9%).

2-Amino-4-arylamino-6-dialkylaminoalkylamino-5-substituted Pyrimidines.—The appropriate 4-chloro-2-amino-6-arylamino-5-substituted pyrimidine was heated with excess of dialkylaminoalkylamine and a trace of potassium iodide for 6 hours at 160—165°. The resulting mixture was dissolved in dilute hydrochloric acid and the solution filtered, if necessary, from insoluble material. The filtrate was added to excess

TABLE I.
2-Amino-4-arylamino-6-dialkylaminoalkylaminopyrimidines.

Ref. No.	Substituent at 4.	Substituent at 6.	Solvent; appearance.	M. p.	Formula.	Analysis.	
						Found, %.	Required, %.
3925	C ₆ H ₄ Cl (p)	CH ₃ , NMe ₂	Benzene	139—140°	C ₁₄ H ₁₉ N ₅ Cl	C, 55.1; H, 6.4; N, 26.8	C, 54.8; H, 6.2; N, 27.4
3939	C ₆ H ₄ Cl (p)	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°); prisms	109—111	C ₁₇ H ₂₃ N ₅ Cl	C, 59.0; H, 7.7; N, 23.9	C, 58.5; H, 7.2; N, 24.1
3923	C ₆ H ₄ Cl (p)	[CH ₂] ₃ .NMe ₂	Benzene; plates	132—134	C ₁₅ H ₂₁ N ₅ Cl	C, 56.4; H, 6.6; N, 25.7	C, 56.2; H, 6.6; N, 26.2
3934	C ₆ H ₄ Cl (p)	CHMe[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°); prisms	128—130	C ₁₉ H ₂₉ N ₅ Cl	C, 60.9; H, 7.9; N, 21.8	C, 60.5; H, 7.7; N, 22.3
3913	C ₆ H ₄ .OMe (p)	[CH ₂] ₃ .NEt ₂	Benzene; plates	123—125	C ₁₇ H ₂₅ ON ₅	C, 62.3; H, 7.5; N, 25.4	C, 61.8; H, 7.9; N, 26.45
3922	C ₆ H ₄ .Me (p)	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°); tables	108—109	C ₁₇ H ₂₅ N ₅	C, 65.0; H, 8.8; N, 26.2	C, 65.0; H, 8.3; N, 26.8

TABLE II.
2-Amino-4-p-chloroanilino-6-dialkylaminoalkylamino-5-substituted Pyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis.	
						Found, %.	Required, %.
4072	Et	[CH ₂] ₃ .NEt ₂	Light petroleum (b. p. 60—80°)	71—72°	C ₁₈ H ₂₇ N ₅ Cl	C, 60.6; H, 7.5; N, 22.3	C, 60.5; H, 7.7; N, 22.3
4109	Et	[CH ₂] ₃ .NEt ₂	Light petroleum (b. p. 80—100°)	102—103	C ₁₉ H ₂₉ N ₅ Cl	C, 58.8; H, 7.1; N, 24.0	C, 58.5; H, 7.2; N, 24.1
4108	Et	[CH ₂] ₃ .NMe ₂	Light petroleum (b. p. 100—120°)	130—132	C ₁₇ H ₂₃ N ₅ Cl	C, 64.1; H, 7.6; N, 27.3	C, 64.6; H, 7.6; N, 27.8
4133	Ph	[CH ₂] ₃ .NEt ₂	Benzene	151—152	C ₁₉ H ₂₇ N ₅	C, 64.5; H, 6.4; N, 20.0	C, 64.3; H, 6.6; N, 20.4
4199	Ph	[CH ₂] ₃ .NMe ₂	Alcohol	170—171	C ₂₁ H ₂₇ N ₅ Cl	C, 63.9; H, 6.4; N, 20.5	C, 63.6; H, 6.3; N, 21.2
4200	Ph	[CH ₂] ₃ .NEt ₂	Alcohol	157—158	C ₂₁ H ₂₉ N ₅ Cl	C, 64.6; H, 6.5; N, 20.4	C, 65.0; H, 6.8; N, 19.8

All these compounds formed colourless laminae, except the last two which were obtained as colourless thick prisms. * 4-p-Cyanoanilino-compound.

TABLE III.
4-Chloro-2-amino-6-aminoalkylaminopyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis.	
						Found, %.	Required, %.
4284	H	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°) ¹	93—95°	C ₁₀ H ₁₈ N ₅ Cl	C, 49.6; H, 7.0; N, 28.4	C, 49.3; H, 7.4; N, 28.7
4552	H	[CH ₂] ₃ .NEt ₂	Light petroleum (b. p. 100—120°) ²	86—87	C ₁₁ H ₂₀ N ₅ Cl	C, 51.5; H, 7.8; N, 26.8	C, 51.3; H, 7.8; N, 27.2
4395	Et	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°) ²	105—106	C ₁₂ H ₂₂ N ₅ Cl	C, 53.2; H, 7.6; N, 25.2	C, 53.4; H, 8.1; N, 25.8
4442	Et	[CH ₂] ₃ .NEt ₂	Benzene ³	115—116	C ₁₃ H ₂₄ N ₅ Cl	C, 54.4; H, 8.6	C, 54.6; H, 8.4
4441	Et	[CH ₂] ₃ .N < [CH ₂] ₄ > CH ₂	Toluene ²	170—171	C ₁₄ H ₂₄ N ₅ Cl	C, 56.9; H, 8.2	C, 56.8; H, 8.1
4395	Ph	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°) ³	138—139	C ₁₆ H ₂₂ N ₅ Cl	C, 59.6; H, 6.8; N, 21.7	C, 60.1; H, 6.9; N, 21.9
4320	Ph	[CH ₂] ₃ .NEt ₂	Benzene-light petroleum (b. p. 60—80°) ³	131—132	C ₁₇ H ₂₄ N ₅ Cl	C, 61.2; H, 6.7; N, 21.0	C, 61.2; H, 7.2; N, 21.0
4415	Ph	[CH ₂] ₃ .N < [CH ₂] ₄ > CH ₂	Benzene ³	151—152	C ₁₈ H ₂₄ N ₅ Cl	C, 62.5; H, 6.4; N, 19.6	C, 62.5; H, 6.9; N, 20.3

¹ Colourless flat needles. ² Colourless laminae. ³ Colourless prisms.

1364 γ -6-Methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylidenecrotonic Acid.

of sodium hydroxide and the precipitated product either filtered off or (if liquid) extracted with chloroform. In either case purification was effected by extraction with 5% acetic acid and reprecipitation with sodium hydroxide. The precipitated product was collected and dried, or extracted with chloroform and the dried extract evaporated, and then crystallised. The compounds prepared are given in Table II.

4-Chloro-2-amino-6-aminoalkylaminopyrimidines.—The requisite 4 : 6-dichloro-2-aminopyrimidine was mixed with the aminoalkylamine (1 mol.) and acetic acid (1 mol.), and heated at 100–110° (115–120° in the case of the 5-phenyl compounds) for 3 hours. The cooled mixture was lixiviated with dilute hydrochloric acid and the solution filtered from unchanged pyrimidine. Addition of sodium hydroxide to the filtrate precipitated the product which was isolated either by filtration or by extraction with ether and then purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. If solid, the product was filtered off and dried; otherwise, it was extracted with ether, and the solution dried and evaporated. The product was then crystallised. Details of the compounds prepared are given in Table III.

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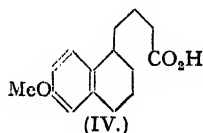
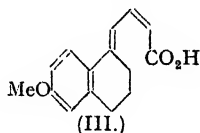
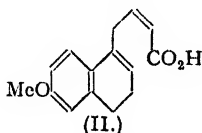
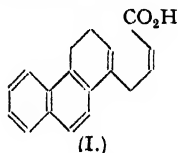
[Received, December 16th, 1946.]

252. γ -6-Methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylidenecrotonic Acid.

By WALTER C. J. ROSS.

γ -6-Methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylidenecrotonic acid has been prepared and its structure elucidated by oxidative degradation and by measurement of its ultra-violet absorption spectrum. The acid can be used in a convenient new synthesis of 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene.

It has been shown that γ -bromocrotonic esters can be used in the Reformatsky reaction in the same way as α -bromo-esters (Fuson, Arnold, and Cooke, *J. Amer. Chem. Soc.*, 1938, **60**, 2272; Ziegler, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 120) and this method has recently been applied by Cook and Schoental (*J.*, 1945, 288), who suggested the formula (I) for the compound obtained from 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene.



The reaction has now been applied to 6-methoxy-1-tetralone, an acid, $C_{15}H_{16}O_3$, m. p. 189–190°, being obtained after the hydrolysis of the ester first formed. By analogy it was regarded as having structure (II). However, the acid exhibits absorption maxima (in chloroform solution) at 2490 Å. and 3480 Å., $\epsilon = 10,300$ and 30,000 respectively. These figures are in much better agreement with a structure such as (III), since this contains a more extended system of conjugation, though the wave-length of the primary maximum is rather higher than would be expected for even this system—this fact could possibly be ascribed to the “exocyclic” of one of the double bonds. Structure (III) is also supported by the fact that when the acid is oxidised by alkaline potassium permanganate an 80% yield of 6-methoxy-1-tetralone is obtained. Rearrangement of the double bonds is very unlikely under the mild conditions of the oxidation and so the new acid is regarded as γ -6-methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylidenecrotonic acid (III).

When the acid is heated at 280–300° with palladium-black, a 55% yield of γ -6-methoxy-1-naphthylbutyric acid is obtained. If the methyl ester of (III) is similarly heated and the product is hydrolysed, an almost quantitative yield of the naphthalenic acid is obtained. Cyclisation of the acid thus formed yields 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene (Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 284) which is a useful intermediate in the production of synthetic hormones, particularly those of the doisyolic acid series (Heer, Billeter, and Miescher, *Helv. Chim. Acta*, 1945, **28**, 1342); the method now described is a very convenient one for the preparation of this ketone.

Reduction of the acid (III) in acetic acid–ethanol solution using a palladium catalyst, or in aqueous alkaline solution using a Raney nickel catalyst, gives a high yield of γ -6-methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylbutyric acid (IV), and when heated with sulphur at 200° this is converted into γ -6-methoxy-1-naphthylbutyric acid (compare Haberland, *Ber.*, 1936 **69**, 1380). These reactions provide an alternative route for the conversion of the acid (III) into 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene.

EXPERIMENTAL.

(M. ps. were determined in sealed capillaries and are uncorrected.)

γ -6-Methoxy-1:2:3:4-tetrahydro-1-naphthylidenecrotonic Acid (III).—Zinc wool (35 g.) was placed in a large flask, dry benzene (400 c.c.) containing mercuric chloride (100 mg.) added, and the mixture warmed for 15 minutes. 6-Methoxy-1-tetralone (94 g.) was added and then ethyl γ -bromocrotonate (114 g., b. p. 80–85°/2 mm., prepared essentially by the method of Ziegler *et al.*, *Annalen*, 1942, 551, 80) was run in at such a rate that the reaction proceeded at a vigorous but controllable pace. The mixture was heated under reflux for a further hour after all the ester had been added, and by this time a deep red complex had separated and most of the zinc had dissolved. The mixture was cooled and decomposed by shaking it with 2N-hydrochloric acid (500 c.c.). The product was extracted with ether, and the extract was washed with water, evaporated, and heated under reflux for 2 hours with potassium hydroxide (50 g.) in methanol (500 c.c.) and water (100 c.c.). The mixture was diluted with water and extracted with ether—this extract contained unchanged ketone (50 g.)—and then the aqueous layer was acidified, a yellow precipitate of the unsaturated acid being formed. The solid (28 g.) was collected and recrystallised from acetone or methanol; it formed hard prisms, m. p. 189–190° (Found: C, 73.2; H, 6.8. $C_{15}H_{14}O_3$ requires C, 73.7; H, 6.6%).

The methyl ester was prepared by the action of an ethereal solution of diazomethane on the acid or by refluxing the acid (10 g.) with methanol (80 c.c.) containing acetyl chloride (10 c.c.) for one hour (compare Riegel and Moffat, *J. Amer. Chem. Soc.*, 1943, 65, 1971). In each case the crystalline residue obtained after evaporating off the solvents was recrystallised from methanol, giving lemon-yellow prismatic plates of the ester, m. p. 85–86° (Found: C, 74.2; H, 7.2. $C_{16}H_{16}O_3$ requires C, 74.4; H, 7.0%).

Oxidation of Acid (III).—The acid (2 g.) was dissolved in excess of 2N-sodium carbonate, and finely powdered potassium permanganate was added to the stirred solution until the supernatant liquid remained coloured. The product was extracted with ether, and the extract dried (Na_2SO_4) and evaporated. 6-Methoxy-1-tetralone (1.15 g., 80%), m. p. 78–79° (undepressed by admixture with an authentic specimen of m. p. 79°), was obtained.

γ -6-Methoxy-1-naphthylbutyric Acid.—The methyl ester of (III) (10 g.) was heated at 280–300° for 1 hour in a metal-bath with palladium-black (700 mg.). The product was dissolved in methanol (60 c.c.), potassium hydroxide (10 g. in 10 c.c. of water) added, and the mixture heated under reflux for 2 hours. The cooled solution was filtered and then acidified with dilute hydrochloric acid; the naphthalenic acid (9.7 g.), m. p. 149–151°, was thus precipitated (Cohen, Cook, and Hewett, *J.*, 1936, 52, give m. p. 150–151°).

Reduction of Acid (III).—(a) The acid (1.0 g.) was dissolved in ethanol (75 c.c.) and acetic acid (10 c.c.), and after addition of palladium-strontium carbonate (500 mg. containing 5% palladium) the solution was shaken in an atmosphere of hydrogen. Hydrogen was rapidly absorbed, and after $\frac{1}{2}$ hour the theoretical volume of gas (calculated for the reduction of two double bonds) had been taken up. The solvents were evaporated, and the oily residue was crystallised from light petroleum (b. p. 60–80°), giving the required acid, m. p. 76–78° (900 mg.) (Haberland, *loc. cit.*, gives m. p. 79°).

(b) The acid (2.5 g.) was dissolved in water (25 c.c.) containing sodium hydroxide (6 c.c. 2N), Raney nickel catalyst (1 g.) added, and the mixture shaken in an atmosphere of hydrogen. The theoretical volume of hydrogen was absorbed in 3 hours. After filtration, the solution was acidified, and the oily precipitate crystallised from light petroleum. In this way 2.1 g. of the required acid, m. p. 77°, were obtained.

When the acid prepared by either method was heated at 200° for 3 hours with $\frac{1}{2}$ its weight of sulphur, γ -6-methoxy-1-naphthylbutyric acid, m. p. 149–150°, was obtained.

The author's thanks are due to Professor J. W. Cook, F.R.S., for suggesting this method of preparing 1-keto-7-methoxy-1:2:3:4-tetrahydrophenanthrene, to Dr. E. A. Braude for measuring the absorption spectrum, and to Organon Laboratories Ltd. for permission to publish the results.

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[Received, December 19th, 1946.]

253. The Structure of Anhydrotetronic Acid.

By D. H. MARRIAN, P. B. RUSSELL, A. R. TODD, and W. S. WARING.

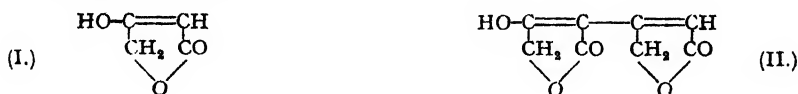
Anhydrotetronic acid, obtained by refluxing tetronic acid in aqueous solution, is shown by degradative studies to have structure (II).

IN the course of investigations in this laboratory on the hatching factor for the potato eelworm (*Heterodera rostochiensis* Wollenweber) produced by certain host species of *Solanaceae* it was observed that anhydrotetronic acid possessed the property of hatching eelworm cysts (Calam, Todd, and Waring, to be published elsewhere). Since this acid was at that time the only active synthetic substance known, it was a matter of considerable importance for further work that its precise structure should be ascertained, and the investigation described in this paper was accordingly carried out.

Anhydrotetronic acid was first described by Wolff and Schwabe (*Annalen*, 1896, 291, 251), who obtained it as colourless crystals containing one molecule of water of crystallisation by heat,

ing an aqueous solution of tetronic acid (I). The anhydrous acid, $C_6H_6O_5$, was monobasic and had m. p. 263° (decomp.). Later Wolff (*Annalen*, 1901, **315**, 162) showed that it contained in all probability a reactive methylene group, since with aliphatic and aromatic aldehydes it gave alkylidene- or arylidene-bisanhydrotetronic acids; analogous compounds are obtained from tetronic acid on similar treatment. No further examination of anhydrotetronic acid seems to have been made.

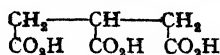
Anhydrotetronic acid, like tetronic acid, owes its acidic properties to an enolic hydroxyl group; it gives a maroon colour with ferric chloride and couples readily with diazonium compounds. On treatment with diazomethane it gives a neutral methyl ether giving no ferric reaction, and on bromination it yields a *mono-bromo-derivative*. It shows strong selective light absorption in the ultra-violet region, and hydrolytic titration at 100° with $N/100$ -sodium hydroxide shows only 20% of the uptake expected for one lactone group. Under optimum conditions anhydrotetronic acid is formed in a yield of only *ca.* 33% by heating aqueous solutions of tetronic acid, but when the water is replaced by aqueous morpholine reaction proceeds rapidly and the yield is almost quantitative. These facts suggest that anhydrotetronic acid has structure (II), but, especially since no analogous compound is obtained under similar conditions from either α - or γ -substituted tetronic acids, it was considered desirable to establish the validity of this structure by degradative methods.



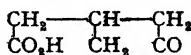
Oxidation of anhydrotetronic acid with potassium permanganate gave oxalic acid, while fusion with potassium hydroxide yielded both oxalic and acetic acids. Refluxed with dilute sulphuric acid, anhydrotetronic acid evolved 1 mol. of carbon dioxide during 15 hours; the product, a resinous acid, gave a crystalline *p*-phenylphenacyl ester, but was not identified. Hydrogenation of anhydrotetronic acid in methanolic solution with a platinum catalyst proceeded rather slowly and ceased when about 2.5 mols. of hydrogen had been taken up. The product was not homogeneous and could be readily separated into neutral and acidic fractions. The acidic fraction was semi-solid, and no crystalline derivative could be prepared from it. It clearly contained an enolic hydroxyl group, since it gave a maroon ferric reaction and showed selective light absorption at 2330 \AA . (ϵ , 5000). Titration of the crude fraction gave an equivalent of 221, and hydrolytic titration caused a further uptake of alkali equivalent to 93% of that required for a second acid grouping. The failure to isolate any crystalline derivative from the material suggested that it was probably a mixture of acids; it was accordingly oxidised with potassium permanganate in the hope of obtaining identifiable fragments which would give some clue to its nature. Oxidation was at first rapid but slowed down later and was stopped when the equivalent of 6 atoms of oxygen had been used up. From the product, tricarballic acid (propane-1:2:3-tricarboxylic acid) (III) and homoparaconic acid (homopilosinic acid, butanolide-2-acetic acid) (IV) were isolated. The isolation of (IV) is significant, since it is clear that in its formation the portion of the anhydrotetronic acid molecule (and of the enolic reduced acid) containing the enolic hydroxyl group has been destroyed. The lactone ring of (IV) is derived from one of the tetronic acid residues present in the starting material, and it is evident that the β -carbon atom in this residue must have been joined to the α -position of the second (enolic) residue in anhydrotetronic acid.

The distilled neutral fraction from the hydrogenation of anhydrotetronic acid was stable to permanganate and showed no selective light absorption in the ultra-violet region. It was evidently a mixture, since it gave analytical values lying between those corresponding to $C_8H_{10}O_4$ and $C_8H_{14}O_5$, and hydrolytic titration gave an equivalent of 101. Treatment with hydrazine gave a mixture of isomeric dihydrazides, $C_8H_{14}O_4N_4$, which was separated into one pure *dihydrazide*, m. p. 155° , which was sparingly soluble in methanol, and a mixture of more soluble dihydrazides, m. p. 125 – 140° . Both the dihydrazide, m. p. 155° , and the isomer mixture were oxidised by periodate, 3 mols. of reagent being consumed in each case. Since model experiments showed that hydrazides are oxidised by periodate according to the equation $2R\cdot CO\cdot NH\cdot NH_2 + 2O = R\cdot CO\cdot NH\cdot NH\cdot COR + N_2 + 2H_2O$, it can be deduced that the dihydrazides obtained above contain one α -glycol grouping. From these facts it is concluded that the neutral fraction from the hydrogenation contained the methyl ester of a lactonic hydroxy-acid, $C_8H_{12}O_4$, and the corresponding dilactone in their various stereoisomeric modifications; treatment of such a mixture with hydrazine would obviously yield a mixture of stereo-

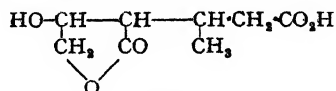
isomeric dihydrazides. It may further be inferred that the potential carboxyl groups of the two tetronic acid molecules involved in the formation of anhydrotetronic acid are still present in the latter compound, and that the ring which has been opened by hydrogenolysis to form the acid $C_6H_{12}O_4$ is not the one bearing the enolic hydroxyl of anhydrotetronic acid. The acid $C_6H_{12}O_4$ is therefore regarded as a β -(2-hydroxybutanolide-1)-butyric acid (V).



(III.)

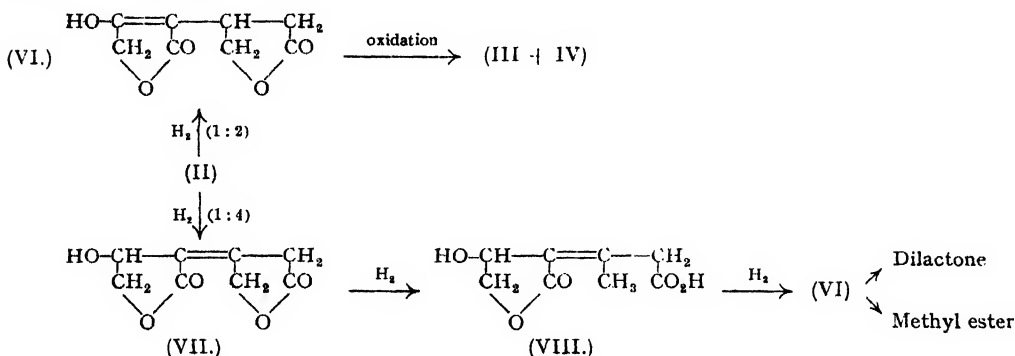


(IV.)



(V.)

These results suffice to establish beyond reasonable doubt structure (II) for anhydrotetronic acid. The course of the hydrogenation described above is explained on the basis of this structure according to the scheme given below. Addition of hydrogen in the 1 : 2-position of the conjugated system would give (VI), probably the major component of the acidic fraction, since as a substituted tetronic acid its further hydrogenation would be slow (Kumler, *J. Amer. Chem. Soc.*, 1938, 60, 859); oxidation of (VI) would yield tricarballic and homoparaconic acids. Addition of hydrogen in the 1 : 4-position would yield (VII) as initial product in which ready hydrogenolysis of one lactone ring would occur giving (VIII). Further hydrogenation of (VIII) would yield the lactonic acid (V), which either lactonises or is esterified by the solvent under the conditions of hydrogenation (cf. Waser, *Helv. Chim. Acta*, 1925, 8, 117) giving the neutral fraction isolated.



The fact that α -substituted tetronic acids are recovered unchanged after treatment under conditions leading to the formation of anhydrotetronic acid (II) from tetronic acid is readily understood, but failure to prepare corresponding anhydro-acids from γ -substituted tetronic acids is rather surprising. On heating an aqueous solution of tetronic acid, the formation of anhydrotetronic acid can be followed by the rise in equivalent. Under similar conditions a definite, although smaller, rise in equivalent was observed with γ -methyltetronic acid (54% increase in 90 minutes) or $\gamma\gamma$ -dimethyltetronic acid (7% increase in 90 minutes), indicating that some condensation had occurred; no anhydro-acids could be isolated from the resulting solutions, nor could the starting material be recovered. Like α -acetyltetronic acid (Baker, Grice, and Jansen, *J.*, 1943, 241), anhydrotetronic acid ($pK = 1.99$) is a much stronger acid than tetronic acid which has $pK = 3.76$ (Kumler, *loc. cit.*), and as in the case of α -acetyltetronic acid this increase can be attributed to the increased resonance possibilities in the ionised form. Structural models show that substitution on the γ -carbon atom of tetronic acid would prevent the derived anhydro-acid from assuming a planar configuration, with consequent loss of resonance possibilities. As a result the derived anhydro-acid would be less stable and might decompose rapidly after formation or the condensation might take a different course after the initial aldol stage; either possibility would explain the experimental results.

EXPERIMENTAL.

Anhydrotetronic Acid.—(1) *In water.* Tetronic acid (5 g.) in water (15 c.c.) was refluxed for 10 minutes. On cooling, anhydrotetronic acid separated in small crystals (1.6 g.), m. p. 261° . Recrystallised from water it had m. p. 263° (decomp.).

(2) *In aqueous morpholine.* Tetronic acid (1.75 g.) in water (10 c.c.) and morpholine (1 c.c.) were refluxed for 10 minutes; the solution was cooled and acidified with sulphuric acid, giving 1.6 g. of

anhydrotetronic acid, m. p. 260° (decomp.). Recrystallised from water it had m. p. 263° (decomp.). Light absorption in alcohol: maxima at 3100 Å. (ϵ , 14,200) and 2560 Å. (ϵ , 9600).

Methyl Ether of Anhydrotetronic Acid.—Anhydrotetronic acid (200 mg.) in cold methanol (25 c.c.) was treated with excess of ethereal diazomethane. The solution was left overnight and then evaporated under reduced pressure, the residual oil was diluted with ether, and the brownish needles were collected and recrystallised from methanol (charcoal). The ether formed colourless plates, m. p. 185° (colours on heating) [Found: C, 55.0; H, 4.1; OMe, 16.1. $C_9H_8O_6$ requires C, 55.1; H, 4.1; OMe (1), 15.8%].

Bromination of Anhydrotetronic Acid.—Anhydrotetronic acid (100 mg.) in a few drops of water was covered with chloroform (2 c.c.), and a solution of bromine in chloroform (1 g. of bromine in 10 c.c. of chloroform) added slowly with shaking. Reaction appeared to be complete when 0.7 c.c. of solution had been added. The solution was filtered and allowed to evaporate at room temperature; a glass resulted which gradually solidified on standing to a hard white powder, m. p. 144–146°. Attempts to recrystallise the bromo-derivative failed [Found: C, 34.5; H, 2.7. $C_9H_5O_6Br$ requires C, 34.4; H, 2.5%].

Oxidation of Anhydrotetronic Acid with Potassium Permanganate.—Anhydrotetronic acid (404 mg.) in water (20 c.c.) was treated with potassium permanganate solution (1.5 g. in 100 c.c. of solution), of which 10 c.c. were taken up (ca. 5 atoms of oxygen). The solution was filtered and acidified with dilute sulphuric acid. Volatile acid corresponding to 8.5 c.c. of N/10-sodium hydroxide was removed by steam distillation. The residual solution was exhaustively extracted with ether, evaporation of which gave a yellow solid (340 mg.). Recrystallised from ether it gave colourless prisms, m. p. 102°; these were concluded to be oxalic acid from equivalent determination (Found: equiv., 64. Calc. for $C_2H_2O_4 \cdot 2H_2O$: equiv., 63) and from the fact that they gave an insoluble calcium salt.

Potassium Hydroxide Fusion of Anhydrotetronic Acid.—Anhydrotetronic acid (250 mg.), potassium hydroxide (1 g.), and water (1 c.c.) were heated in a nickel crucible until fused. The melt was deep red at first but became yellow as the temperature was raised. When the temperature reached 250°, a further quantity (1 g.) of potassium hydroxide was added. The temperature was then raised to 300° and maintained for 10 minutes. The cooled melt was dissolved in water, acidified, and extracted with ether, evaporation of which left a brownish solid smelling of acetic acid. The residue was dissolved in water and the volatile acid removed by steam distillation. The steam distillate required 7.85 c.c. of N/10-sodium hydroxide (equivalent to 47.1 mg. of acetic acid; 0.7 mol.) for neutralisation. After neutralisation the distillate was evaporated and the sodium salt refluxed with *p*-phenylphenacyl bromide in alcohol. On cooling a *p*-phenylphenacyl ester separated. Recrystallised from alcohol it had m. p. 108–109°, undepressed by the *p*-phenylphenacyl ester of acetic acid.

Extraction of the steam distillation residue gave 126 mg. of oxalic acid which, recrystallised from ether, had m. p. 98–100° (Found: equiv., 62). The amount of oxalic acid obtained corresponded to 0.7 mol.

Treatment of Anhydrotetronic Acid with Sulphuric Acid.—Anhydrotetronic acid (508 mg.) was refluxed with N-sulphuric acid in a stream of nitrogen, the carbon dioxide evolved being collected in barium hydroxide solution.

Time (hrs.)	0.5	2.5	6.5	14.5	16.5
CO ₂ (% mol.)	5.6	27.9	55.0	108.0	110.0

The reaction mixture was made alkaline and extracted with ether; no neutral fraction was obtained. On reacidification of the solution and extraction with ether it gave a brown resinous oil (400 mg.) (equiv., 135). The resin reduced Tollens's reagent and gave a positive Legal reaction; with ferric chloride it gave a weak green colour. When the acid (50 mg.) was treated with *p*-phenylphenacyl bromide in the usual manner it gave a colourless crystalline ester, m. p. 156–158° after recrystallisation from ethanol (Found: C, 75.3; H, 5.5. $C_{21}H_{18}O_4$ requires C, 75.4; H, 5.4%). Anhydrotetronic acid was recovered unchanged after being heated on the steam-bath for 2 hours with 2% oleum.

Hydrogenation of Anhydrotetronic Acid.—Anhydrotetronic acid (3 g.) in methanol (75 c.c.) was shaken with hydrogen in presence of platinum (from 0.25 g. of platinum oxide), 859 c.c. being absorbed in 4 hours. The catalyst was then removed and the methanol evaporated; water was added and the solution neutralised with N/10-sodium hydroxide and extracted continuously with ether for 24 hours. The ether was dried and removed, giving a neutral residue (0.9 g.), which distilled as a pale yellow viscous oil, b. p. 180–190° (bath temp.)/10⁻⁵ mm., stable to potassium permanganate in the cold [Found: C, 54.5; H, 6.6; OMe, 4.5; active H₂, 0.22; *M* (Rast), 210; equiv. by hydrolytic titration, 101, 98. Calc. for $C_8H_{14}O_6$: C, 53.5; H, 6.9; OMe (1), 15.3; active H₂ (1), 0.50%; *M*, 202; equiv. (2 potential CO₂H), 101. Calc. for $C_8H_{10}O_4$: C, 56.4; H, 5.9%; *M*, 170; equiv., 85]. Acidification of the alkaline solution followed by extraction with ether gave a semi-solid acid fraction (2 g.) (1st equiv., 221 in cold; 2nd equiv., 198 in warm. Calc. for $C_8H_8O_6$: 1st equiv., 184; 2nd equiv., 184). The substance was acid to Congo-red and was rapidly oxidised by permanganate in the cold. It was soluble in cold alkali and gave a maroon colour with ferric chloride. Light absorption in alcohol: maximum at 2330 Å. (ϵ , 5000).

Hydrazides from Neutral Fraction from Hydrogenation.—The above neutral fraction (0.2 g.) was heated with hydrazine (1 g.) on a steam-bath for 3½ hours. Excess of hydrazine was removed under reduced pressure leaving a crystalline residue. Extraction with boiling methanol gave a crystalline almost insoluble dihydrazide, m. p. 155° (Found: C, 40.9; H, 7.5; N, 23.5. $C_8H_{14}O_4N_4$ requires C, 41.1; H, 7.7; N, 23.9%). The methanol extract was diluted with ethyl acetate and yielded a mixture of isomeric dihydrazides, m. p. 125–140° (Found: N, 23.9. Calc. for $C_8H_{14}O_4N_4$: N, 23.9%). The dihydrazide, m. p. 155° (13.4 mg.; 0.0573 $\times 10^{-3}$ mol.), in water was treated with 1 c.c. of 0.235M-sodium periodate; 0.173 $\times 10^{-3}$ mol. of periodate was absorbed (i.e., 3.02 mols. of periodate per mol. of dihydrazide). The mixed dihydrazides (21.0 mg.) were treated with 2 c.c. of 0.235M-sodium periodate and used up 1.095 c.c. (i.e., 2.89 mols. per mol.).

Oxidation of Benzhydrazide with Periodate.—Benzhydrazide (131.5 mg.; 0.968 $\times 10^{-3}$ mol.) treated with 5 c.c. of 0.235M-periodate used up 4.05 c.c., i.e., 0.982 mols. per mol. The solid which separated, recrystallised from aqueous methanol, had m. p. 238–239° alone or mixed with dibenzoylhydrazine, m. p. 239°.

Oxidation of the Acid Fraction from Hydrogenation.—The acid fraction (1.17 g.) from the above hydrogenation was dissolved in acetone (20 c.c.) and water (20 c.c.), and 2% potassium permanganate was added dropwise with stirring at room temperature. When 3 atoms of oxygen had been taken up the rate of oxidation slowed considerably; in all 6 atoms of oxygen were added. The solution was filtered, acidified, and extracted with ether. On standing, crystalline material separated from the ether, m. p. 157–159°, undepressed in admixture with authentic tricarballic acid (m. p. 158–159°). The solution was evaporated, giving an oil which subsequently crystallised and then had m. p. 70–73°. Recrystallised from chloroform-carbon disulphide it had m. p. 78°. Sublimation in a vacuum (70°/10⁻⁵ mm.) gave colourless prisms, m. p. 80–81.5° (Found: C, 50.2; H, 5.9. Calc. for C₆H₃O₄: C, 50.0; H, 5.6%). The m. p. was not depressed on admixture with authentic homoparaconic acid (m. p. 82–82.5°; Polyakova, Preobrazhenskii, and Preobrazhenskii, *J. Gen. Chem. Russia*, 1939, 9, 1402).

Grants from the Agricultural Research Council in aid of this work are gratefully acknowledged.

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[Received, December 19th, 1946.]

254. *Synthesis of ω -Aminoalkyl Cyanides.*

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A number of ω -aminoalkyl cyanides have been prepared by interaction of ω -bromoalkyl cyanides with potassium phthalimide followed by deacylation of the resulting ω -cyanoalkyl-phthalimides with hydrazine. The synthetic method would appear to be general for the production of any ω -aminoalkyl cyanide.

THE literature relating to aminoalkyl cyanides is not extensive. Aminomethyl cyanide (Klages, *J. pr. Chem.*, 1902, 65, 188; Anslow and King, *J.*, 1929, 2463; Menge, *J. Amer. Chem. Soc.*, 1934, 56, 2197), 1-aminoethyl cyanide (Dubsky, *Ber.*, 1916, 49, 1048), 2-aminoethyl cyanide (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, 66, 725), and 2-aminopropyl cyanide (Bruylants, *Bull. Soc. chim. Belg.*, 1923, 32, 256) have been prepared by special methods not of general application. In addition, ω -aminoamyl cyanide has been prepared by the high pressure semihydrogenation of adiponitrile (U.S.P.P. 2,208,598, 2,234,566).

ω -Aminoalkyl cyanides were required for the synthesis of a group of new aminoalkyl substituted heterocycles, and a convenient and general method was sought for their preparation. It has been found that ω -cyanoalkylphthalimides, readily available from potassium phthalimide and ω -bromoalkyl cyanides or from ω -bromoalkylphthalimides and potassium cyanide, can be deacylated with hydrazine by the Ing and Manske reaction (*J.*, 1926, 2348) with production of the aminoalkyl cyanide in substantial yield. It is of interest that the intermediate formed by the interaction of hydrazine and the phthalimidoalkyl cyanide yields phthalyl hydrazide and the aminoalkyl cyanide on acidification with hydrochloric acid without prolonged hydrolysis; this accords with the recent observations of Mosher (*J. Amer. Chem. Soc.*, 1946, 68, 1565) on the decomposition of similar compounds. Deacylation with constant-boiling hydrochloric acid or by the modified method of Gabriel (*cf. Ber.*, 1911, 44, 3632) with 5*N*-hydrochloric acid *via* the phthalamic acid is not possible owing to simultaneous hydrolysis of the cyano-group. Since various $\omega\omega$ -alkylenediols are now available which are readily converted through the alkylene dibromides into the corresponding ω -bromoalkyl cyanides, and an $\omega\omega$ -alkylene dibromide, Br[CH₂]_{*n*}Br, can be transformed into the ω -bromoalkyl cyanide, Br[CH₂]_{*n*+1}CN (*cf. Willstätter and Ettlinger, Annalen*, 1903, 326, 99; Leuchs, *Ber.*, 1911, 44, 1510; Cheney and Piening, *J. Amer. Chem. Soc.*, 1945, 67, 731; Breslow and Hansen, *ibid.*, p. 686), the method appears to be general for the synthesis of ω -aminoalkyl cyanides.

In this manner 3-amino-*n*-propyl cyanide, 5-amino-*n*-amyl cyanide, and 10-amino-*n*-decyl cyanide have been obtained. Contrary to the impression given by the literature the aminoalkyl cyanides are stable provided they are kept under anhydrous conditions. Protection of the amino-group by acylation allows the terminal cyano-group to undergo its functional reactions—*e.g.*, thioamide, imino-ether, and amidine transformation—and, often, subsequent formation of the 2-(acylamidoalkyl) heterocycle. The synthesis of a series of 2-(ω -aminoalkyl)-thiazoles and -pyrimidines from these acylamidoalkyl cyanides is described in the following paper; the synthesis of a number of 2-(ω -aminoalkyl)-iminazoles and -iminazolines will be reported shortly.

EXPERIMENTAL.

3-Phthalimido-*n*-propyl Cyanide.—A solution of potassium cyanide (75 g.) in water (150 c.c.) was added dropwise during 1½ hours to a stirred refluxing solution of trimethylene dibromide (202 g.) in alcohol (300 c.c.). Stirring at the reflux was continued for a further 1 hour, water (750 c.c.) added, and the solution extracted with chloroform (3 × 150 c.c.). The combined extracts after drying and

distillation yielded recovered trimethylene dibromide (41 g.), b. p. $55^{\circ}/14$ mm., 3-bromopropyl cyanide (45 g.), b. p. $90-92^{\circ}/13$ mm., and tetramethylene dicyanide (17 g.), b. p. $138-140^{\circ}/13$ mm. (cf. Gabriel, *Ber.*, 1889, **22**, 3336).

Potassium phthalimide (60 g.) was refluxed with a solution of 3-bromopropyl cyanide (44 g.) in absolute alcohol (200 c.c.) for 10 hours, alcohol (ca. 100 c.c.) distilled off, and the residual solution poured into water (1 l.). The oil which separated rapidly solidified (56 g.; m. p. 60°); it was collected and recrystallised from dilute methyl alcohol, 3-phthalimidopropyl cyanide being obtained in white plates, m. p. $65-66^{\circ}$ (Found: N, 13.2. $C_{12}H_{16}O_2N_2$ requires N, 13.1%).

3-Amino-n-propyl Cyanide.—Hydrazine hydrate (50% w/w solution; 25.5 g.) was added to a solution of the foregoing phthalimido-cyanide (40 g.) in alcohol (150 c.c.) at 50° and the resulting solution allowed to cool and kept at room temperature for 1 hour. Water (50 c.c.) was added, and the solution rendered just acid to Congo-red by concentrated hydrochloric acid, warmed to 60° , and kept for 2 hours. The insoluble phthalyl hydrazide was removed and the filtrate evaporated at reduced pressure at $<40^{\circ}$ to small volume. The residue was chilled, basified with 10N-sodium hydroxide (150 c.c.), extracted with ether (5×100 c.c.), the ethereal solution dried, and anhydrous alcoholic hydrogen chloride (10% w/w) added in order to precipitate the hydrochloride (10.5 g.; m. p. $134-136^{\circ}$); recrystallisation from anhydrous alcohol gave 3-amino-n-propyl cyanide hydrochloride in white plates, m. p. $138-140^{\circ}$ (Found: N, 23.0; Cl, 29.8. $C_4H_8N_2 \cdot HCl$ requires N, 23.2; Cl, 29.5%). The hydrochloride (20 g.) was added to 10N-sodium hydroxide (50 c.c.) and the whole thoroughly extracted with ether; after drying over potassium carbonate the ethereal solution was distilled, 3-amino-n-propyl cyanide being obtained as a colourless water soluble oil, b. p. $95-97^{\circ}/20$ mm. (Found: N, 33.8. $C_4H_8N_2$ requires N, 33.4%).

3-Benzamidopropyl Cyanide.—Benzoyl chloride (21 c.c.) was added dropwise during $\frac{1}{2}$ hour to a rapidly stirred solution of sodium carbonate (25 g.) and 3-aminopropyl cyanide hydrochloride (20 g.) in water (200 c.c.) at 15° . Stirring at room temperature was continued for 2 hours, and the white insoluble 3-benzamidopropyl cyanide collected, washed with water and dried in a vacuum; yield 25 g., m. p. $74-76^{\circ}$. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in colourless nacreous plates, m. p. $78-80^{\circ}$ (Found: C, 70.0; H, 6.5; N, 15.1. $C_{11}H_{12}ON_2$ requires C, 70.3; H, 6.4; N, 14.9%).

5-Phthalimido-n-amyl Cyanide.—5-Bromopentanecarboxylic acid was obtained by the action of hydrobromic-sulphuric acids on the lactone mixture obtained by the potassium persulphate oxidation of cyclohexanone (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839; Robinson and Smith, *J.*, 1937, 371). This was converted in 86% yield into the amide and the latter into 5-bromoamyl cyanide in 80% yield by the method of Breslow and Hansen (*J. Amer. Chem. Soc.*, 1945, **67**, 686).

Potassium phthalimide (50 g.) was refluxed with a solution of 5-bromoamyl cyanide (45 g.) in anhydrous alcohol (150 c.c.) for 24 hours. Alcohol (ca. 125 c.c.) was distilled off, water (125 c.c.) added, and the solution extracted with ether. Removal of the ether from the dried solution yielded 5-phthalimidoamyl cyanide (52 g.) as an oil which could not be induced to crystallise (cf. Albert, *Ber.*, 1909, **42**, 557).

5-Amino-n-amyl Cyanide.—Hydrazine hydrate (50% w/w aqueous solution; 72 g.) was refluxed with a solution of 5-phthalimidoamyl cyanide (152 g.) in alcohol (300 c.c.) for 1 hour and the solution left overnight. The solid mass was dissolved in water (1000 c.c.), the solution rendered just acid to Congo-red by the addition of 10N-hydrochloric acid (ca. 120 c.c.), and the precipitate of phthalyl hydrazide removed. The filtrate and washings were evaporated to small volume under reduced pressure at $<40^{\circ}$, and the chilled residue was basified with 10N-sodium hydroxide and extracted with chloroform (3×100 c.c.). The extract was dried (K_2CO_3) and distilled, 5-aminoamyl cyanide (52 g.) being obtained as a colourless oil, b. p. $116-118^{\circ}/14$ mm. (Found: N, 24.8. $C_6H_{12}N_2$ requires N, 25.0%).

A solution of the foregoing base (11.1 g.) and sodium carbonate (7.5 g.) in water (100 c.c.) was stirred at 15° and benzoyl chloride (11.3 c.c.) added slowly. Stirring was continued for a further 2 hours, and the precipitated 5-benzamidoamyl cyanide collected, washed with cold water, and dried in a vacuum; yield 18.6 g., m. p. $94-96^{\circ}$. A sample crystallised from benzene-ligroin in colourless acicular prisms, m. p. 98° (Found: C, 72.1; H, 7.4; N, 13.3. Calc. for $C_{13}H_{16}ON_2$: C, 72.2; H, 7.5; N, 13.0%). Von Braun and Steindorff (*Ber.*, 1904, **37**, 2915) prepared this compound from N-benzoylpiperidine and record m. p. 96° (cf. Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, B, 60). A solution of 5-aminoamyl cyanide (2.0 g.) and sodium carbonate (3.5 g.) in 50% acetone (50 c.c.) was stirred at 20° with p-acetamidobenzenesulphonyl chloride (4.2 g.) for 1 hour. The 5-(p-acetamidobenzenesulphonamido)amyl cyanide (5.1 g.; m. p. 112°) was filtered off and washed with water; it separated from dilute methyl alcohol in colourless plates, m. p. 114° (Found: N, 13.8; S, 10.5. $C_{14}H_{18}O_2N_2S$ requires N, 13.6; S, 10.4%).

10-Bromodecyl Cyanide.—A mixture of 10-bromodecanecarboxylic acid (102 g.; Ashton and Smith, *J.*, 1934, 438) and thionyl chloride (150 c.c.) was kept at room temperature for $\frac{1}{4}$ hours and then refluxed for a further $\frac{1}{4}$ hour. The excess of thionyl chloride was distilled off at reduced pressure and the residual oil added slowly to rapidly stirred aqueous ammonia (d 0.88; 1000 c.c.) at 10° . Stirring was continued for a further 2 hours and the pale brown precipitate of 10-bromodecanecarboxylamide (98 g.; m. p. $84-86^{\circ}$) collected, washed with water, and dried in a vacuum. A sample crystallised from benzene in cream plates, m. p. 90° (Found: N, 5.6; Br, 29.8. Calc. for $C_{11}H_{23}ONBr$: N, 5.3; Br, 30.3%). In one preparation the crude acid chloride was distilled and obtained as a colourless oil, b. p. $176-178^{\circ}/1$ mm., but distillation was normally found to be unnecessary.

The foregoing amide (98 g.) was refluxed with thionyl chloride (100 c.c.) for 75 minutes. After removal of the excess thionyl chloride the residue was distilled and yielded 10-bromodecyl cyanide (86 g.) as a pale golden oil, b. p. $158-164^{\circ}/4$ mm. (cf. Trunel, *Compt. rend.*, 1933, **197**, 453) (Found in redistilled sample: N, 5.5; Br, 31.9. $C_{11}H_{23}NBr$ requires N, 5.7; Br, 32.4%).

10-Phthalimidodecyl Cyanide.—10-Bromodecyl cyanide (84 g.) and potassium phthalimide (66 g.) were refluxed with alcohol (200 c.c.) for 24 hours. Alcohol (160 c.c.) was distilled off, and the residue, after the addition of water (500 c.c.), extracted with chloroform (2×150 c.c.). The extract was dried (K_2CO_3) and the chloroform removed to leave 10-phthalimidodecyl cyanide (97 g.) as a brown oil which failed to crystallise.

10-Amino-n-decyl Cyanide.—A solution of the foregoing phthalimidocyanide (76 g.) in methyl alcohol (200 c.c.) was refluxed for 1 hour with 50% w/w hydrazine hydrate (30 g.) and then kept at 20° overnight. Water (1000 c.c.) was added followed by 10N-hydrochloric acid until an acid reaction to Congo-red was obtained, the precipitate removed, and the filtrate evaporated to small volume at reduced pressure at <40°, the residue strongly basified with cold 10N-sodium hydroxide and extracted with chloroform. After drying over potassium carbonate, the chloroform solution yielded 10-amino-decyl cyanide as an amber water-soluble oil (29 g.), b. p. 138–142°/2 mm.; on redistillation it was obtained as a colourless oil, b. p. 136–138°/2 mm. (Found: N, 15.0. $C_{11}H_{22}N_2$ requires N, 15.4%).

Benzoyl chloride (7.8 g.) was added dropwise to a stirred mixture of the foregoing amino-cyanide (10.0 g.), sodium carbonate (10 g.), and water (100 c.c.) at 15°. Stirring was continued for 1 hour, and the precipitated 10-benzamidodecyl cyanide collected, washed with water and dried in a vacuum (15.4 g.; m. p. 54°); it crystallised from benzene-ligroin in colourless needles, m. p. 64° (Found: C, 75.4; H, 9.1; N, 10.0. $C_{18}H_{26}ON_2$ requires C, 75.5; H, 9.1; N, 9.8%).

Interaction of the aminocyanide with *p*-acetamidobenzenesulphonyl chloride in the presence of sodium carbonate in aqueous acetone in the same manner as described above yielded 10-(*p*-acetamidobenzenesulphonamido)decyl cyanide, which separated from aqueous methyl alcohol in colourless needles, m. p. 94° (Found: N, 11.3; S, 8.2. $C_{19}H_{28}O_3N_2S$ requires N, 11.1; S, 8.4%).

Aminomethyl Cyanide Hydrochloride.—Calcium carbonate (50 g.) was added portionwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.; *Org. Synth.*, Coll. Vol. I, 298) in water (200 c.c.). The excess of calcium carbonate and calcium sulphate were filtered off, and the solution acidified to Congo-red with hydrochloric acid and evaporated to dryness at reduced pressure at <40°. The residue was washed with a small amount of cold alcohol and recrystallised from methyl alcohol-diethyl ether, aminomethyl cyanide hydrochloride being obtained in colourless plates, m. p. 144–146°, which slowly turned purple in contact with the air (Found: N, 30.5; Cl, 37.9. Calc. for $C_2H_4N_2 \cdot HCl$: N, 30.3; Cl, 38.4%) (Menge, *loc. cit.*, gives m. p. 165° darkening at 135°).

Benzamidomethyl Cyanide.—Benzoyl chloride (50 g.) was added dropwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.) and sodium carbonate (70 g.) in water (150 c.c.), the temperature not being allowed to exceed 15°. Stirring was continued at room temperature for 8 hours, and the white insoluble benzamidomethyl cyanide collected, washed with water, and dried; yield 44 g., m. p. 136–138°. A sample crystallised from methyl alcohol in colourless rectangular plates, m. p. 142–144° (Found: N, 17.7. $C_6H_9ON_2$ requires N, 17.5%).

***p*-Acetamidobenzenesulphonamidomethyl Cyanide** (cf. Cocker, *J.*, 1940, 1574).—Sodium carbonate (20 g.) was added to a cold rapidly stirred solution of aminomethyl cyanide sulphate (16.4 g.) in water (50 c.c.); acetone (80 c.c.) was added followed by finely divided *p*-acetamidobenzenesulphonyl chloride (20 g.), and the mixture stirred at room temperature for 3 hours. After the addition of water (50 c.c.) the insoluble *p*-acetamidobenzenesulphonamidomethyl cyanide (17 g.; m. p. 190–192°) was collected, washed with water, and dried; a sample separated from ethyl alcohol in colourless leaves, m. p. 192° (Found: N, 16.8; S, 12.8. Calc. for $C_{10}H_{11}O_3N_2S$: N, 16.6; S, 12.7%).

1-Aminoethyl Cyanide (cf. Dubsky, *loc. cit.*).—A solution of potassium cyanide (80 g.) in water (200 c.c.) was added slowly to a stirred mixture of ammonium chloride (72 g.), ether (600 c.c.), and acetaldehyde (32 g.) at 10°. Stirring was continued for 12 hours at 15°, the ether layer separated, and the aqueous layer extracted with ether (2 \times 100 c.c.). The combined ether solutions were completely dried over ignited potassium carbonate, the ether removed, and the residual oil distilled, 1-aminoethyl cyanide (25 g.) being obtained as a colourless oil, b. p. 53–55°/14 mm. A sample which had been kept for 6 months at 20° under anhydrous conditions redistilled at the same b. p. leaving no residue; a sample kept in the presence of moisture became full of crystalline solid after several weeks. The hydrochloride was obtained in colourless needles, m. p. 144–146°, by the addition of absolute ethereal hydrogen chloride to a solution of the base in absolute alcohol (Found: N, 26.7; Cl, 33.3. $C_3H_5N_2 \cdot HCl$ requires N, 26.3; Cl, 33.3%).

1-Benzamidoethyl Cyanide.—Benzoyl chloride (19 g.) was added dropwise to a stirred solution of 1-aminoethyl cyanide (8.6 g.) and sodium carbonate (10 g.) in water (20 c.c.) maintained at 15° by external cooling. Stirring was continued for 10 hours, and the precipitate of 1-benzamidoethyl cyanide (15.0 g.; m. p. 102–104°) collected, washed with cold water and dried in a vacuum; a sample separated from benzene in colourless needles, m. p. 108° (Found: C, 68.9; H, 5.8; N, 16.4. $C_{10}H_{10}ON_2$ requires C, 69.0; H, 5.8; N, 16.1%).

2-Benzamidoethyl Cyanide.—2-Aminoethyl cyanide was obtained by the method of Whitmore *et al.* (*loc. cit.*). The best yields were obtained by standing the mixture of vinyl cyanide and ammonia at ca. 30° for 48 hours in a glass pressure bottle; 120 g. of freshly distilled vinyl cyanide yielded 40 g. of 2-aminoethyl cyanide, b. p. 80–85°/17 mm., and 80 g. of bis-compound, b. p. 200–220°/12 mm. It was found essential to use a 10-inch Vigreux column for removal of the aqueous ammonia since the aminocyanide is slightly volatile in water vapour.

Benzoyl chloride (80 c.c.) and 5N-sodium hydroxide (180 c.c.) were added simultaneously to a rapidly stirred solution of the foregoing amino-cyanide (40 g.) in water (120 c.c.) in such a manner that the mixture was maintained throughout at 10–12° and at pH 8.5–10.0. After the addition (45 minutes) the mixture was stirred at room temperature for a further 2 hours, and the 2-benzamidoethyl cyanide filtered off, washed with dilute sodium carbonate and water, and dried in a vacuum at 20–30°. Yield, 92 g. of a white powder, m. p. 94–96°, which was pure enough for further use; a sample crystallised from 10% alcohol in colourless needles, m. p. 96–98° (Found: N, 16.3. Calc. for $C_{10}H_{10}ON_2$: N, 16.1%).

The authors thank Mr. N. Virgo for some of the analyses.

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[Received, October 21st, 1946.]

255. Synthesis of the 2- ω -Aminoalkyl and 2- ω -Sulphanilamidoalkyl Derivatives of Thiazole and Pyrimidine.

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4 : 6-Dimethyl-2-aminomethylpyrimidine and a series of 4-methyl-2- ω -aminoalkylthiazoles have been synthesised from the acylamidoalkyl cyanides described in the previous communication. From these new bases homologues of 2-sulphanilamido-4-methylthiazole and 2-sulphanilamido-4 : 6-dimethylpyrimidine have been prepared for examination as bacterial inhibitors.

HOMOLOGUES of sulphanilamide containing the homologising methylene chain between the amino-group and the benzene ring and between the latter and the sulphonamide residue have previously been reported (Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099; G.P. 726382; Klarer, *Die Chemie*, 1943, **56**, 10; Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459). In addition, similar homologues of 2-sulphanilamidothiazole (sulphathiazole) and 2-sulphanilamido-4 : 6-dimethylpyrimidine (sulphadimethylpyrimidine) have been prepared (Bergeim and Braker, *loc. cit.*) and shown to possess activities of a rather lower order against experimental *Cl. perfringens* infections than α -aminotoluene-*p*-sulphonamide (marfanil) (Hamre *et alii*, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 170; compare also MacLennan, *Lancet*, 1943, **265**, 123; Schreus and Peltzer, *Klin. Wochenschr.*, 1941, **20**, 1233, 1250; Schreus, *ibid.*, 1942, **21**, 14; Domagk, *ibid.*, p. 448; Klöse and Schrober, *Zentr. Bakt.*, 1942, **149**, 15). It was accordingly of interest to synthesise a series of homologues of sulphathiazole and sulphadimethylpyrimidine in which the homologising chain occupies a position between the sulphonamido-residue and the heterocycle for examination as bacterial inhibitors.

Two methods were employed which would appear to be of general application for the preparation of this type of homosulphathiazole. Conversion of the ω -benzamidoalkyl or ω -phthalimidoalkyl cyanide into the corresponding thioamide, formation of the thiazole ring by condensation with an α -halogeno-aldehyde or -ketone, and hydrolysis of the product readily yielded the 2-(ω -aminoalkyl)thiazole; this was converted by the normal route into the 2-(ω -sulphanilamidoalkyl)thiazole. Alternatively, the ω -acetylsulphanilamidoalkyl cyanide was transformed into the thioamide, the latter treated with the α -halogeno-aldehyde or -ketone, and the resulting 2-(ω -acetylsulphanilamidoalkyl)thiazole deacetylated with aqueous alkali. The overall yields of the 2-aminoalkylthiazoles and 2-(ω -sulphanilamidoalkyl)thiazoles were of a high order with the lower members and also with the highest member of the series. With 5-acylamidoamyl cyanide, however, the normal procedure of hydrogen sulphide addition in the presence of ammonium sulphide gave the corresponding thioamide in yields of the order of only 25%; use of ethanolamine (Yuoh-Fong Chi, *J. Amer. Chem. Soc.*, 1942, **64**, 90) and alkali ethoxide as catalysts (Erlenmeyer, *Helv. Chim. Acta*, 1944, **27**, 412) failed to effect improvement. The α -halogeno-ketones employed were chloroacetone, ethyl α -chloroacetoacetate, ethyl γ -bromoacetoacetate, and ethyl bromopyruvate. It is of interest that a sample of ethyl α -chloroacetoacetate obtained by the action of sulphuryl chloride on ethyl acetoacetate after standing in diffused daylight in a closed bottle for 12 months gave the same high yield of ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate on condensation with benzamidothioacetamide as did the freshly prepared compound, whereas Epprecht (*Annalen*, 1894, **278**, 79) states that ethyl α -bromoacetoacetate is not stable and on standing for several weeks isomerises in part to the γ -bromo-compound.

The 4-methyl-2-aminoalkylthiazoles are stable, distillable oils, very soluble in dilute acid; the 4-methyl-2-sulphanilamidoalkylthiazoles are well-crystallised compounds with much lower melting points than sulphathiazole and with considerably more solubility than the latter in water and dilute organic acids. The displacement of the thiazole ring from its adjacency to the sulphonamido-residue allows the basic function of the heterocycle, masked in 2-acetylsulphanilamidothiazole, to reappear; for example, the 2-acetylsulphanilamidoalkylthiazoles are easily soluble in cold aqueous mineral acid, whereas 2-acetylsulphanilamidothiazole is completely insoluble.

Less success was obtained in the case of the attempted preparation of a range of homosulphamethazines. Both benzamidomethyl cyanide and acetylsulphanilamidomethyl cyanide readily yielded the corresponding imino-ethers and amidines and these condensed with acetylacetone to give 4 : 6-dimethyl-2-benzamidomethyl- and -2-acetylsulphanilamidomethylpyrimidine; hydrolysis of the former with acid and the latter with dilute alkali gave respectively 4 : 6-dimethyl-2-aminomethylpyrimidine and 4 : 6-dimethyl-2-sulphanilamidomethylpyrimidine. Benzamidoacetamidine reacted readily with ethyl cyanoacetate but failed to give the expected

pyrimidine derivative; elimination of ammonia from the amidine residue and the reactive methylene group of the ester occurred with formation of ethyl (1-amino-2-benzamidoethylidene)-cyanoacetate in good yield. With malononitrile, benzamidoacetamidine reacted in the same manner with production of 1-amino-2-benzamidoethylidenemalononitrile; compare the similar condensation of ethyl cyanoacetate with formamidine and with benzamidine in the absence of alkali (Kenner *et alii*, J., 1943, 388). The higher homologues of benzamidoacetamidine could not be induced to condense with acetylacetone under any of the varied reaction conditions employed.

Antibacterial Activities.—Infections of medium and low density with *Streptococcus hæmolyticus* (Aronson) were induced in mice by intraperitoneal inoculation of 0.5 c.c. of a 1 : 2000 dilution of a 24-hours old broth subculture of organisms of different virulence; the M.L.D. of the standard organism was 0.5 c.c. of a 1 : 32,000 dilution of the 24-hour old subculture, while the other organism used had been attenuated until the M.L.D. of the 24-hour old subculture was 0.5 c.c. of a 1 : 8000 dilution. Oral administration of daily divided doses of 200–300 mg./kg. of the 4-methyl-2-sulphanilamidomethylthiazoles, Nos. 1423, 1424, 1432, 1433, 1323, and of the sulphanilamidomethyl-4 : 6-dimethylpyrimidine, No. 1427, failed to give complete protection to the mice; in the controls daily administration of 100 mg./kg. of sulphathiazole or sulphadiazine or 150 mg./kg. of sulphanilamide effected complete protection. All the compounds showed a small but nevertheless definite activity in daily doses of 400 mg./kg.

The activity of these homosulphonamides against *Cl. perfringens* infections in mice will be reported elsewhere.

EXPERIMENTAL.

(The acylamidoalkyl cyanides used are described in the previous paper.)

Benzamidothioacetamide.—Ammonia was passed into methyl alcohol (200 c.c.) until the increase in weight was 20 g., followed by hydrogen sulphide until 40 g. had been absorbed. Benzamidomethyl cyanide (50 g.) was added, and the resulting solution kept in a closed vessel at room temperature for 36–48 hours with occasional shaking. After the addition of water (500 c.c.) and standing for 12 hours, benzamidothioacetamide (40 g.; m. p. 152–154°) separated in small crystals. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in stout colourless prisms, m. p. 154° (Found : N, 14.7; S, 16.6. $C_8H_{10}ON_2S$ requires N, 14.4; S, 16.5%).

4-Methyl-2-benzamidomethylthiazole.—A solution of the foregoing thioamide (31 g.) in methyl alcohol (300 c.c.) and pyridine (25 c.c.) was refluxed with chloroacetone (23 c.c.) for 2 hours. The methyl alcohol was distilled off, water (200 c.c.) added, and the precipitated 4-methyl-2-benzamidomethylthiazole collected (35 g.; m. p. 108°). A sample separated from aqueous methyl alcohol in pale cream needles, m. p. 114–116° (Found : N, 12.3; S, 13.5. $C_{12}H_{12}ON_2S$ requires N, 12.1; S, 13.8%).

4-Methyl-2-aminomethylthiazole.—A solution of 4-methyl-2-benzamidomethylthiazole (35 g.) in 5N-hydrochloric acid (225 c.c.) was refluxed for 3 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to small volume at reduced pressure. The residue was strongly basified with 10N-sodium hydroxide and extracted with ether (3 \times 100 c.c.); after drying over potassium carbonate and distillation, the ethereal extract yielded 4-methyl-2-aminomethylthiazole (13.5 g.) as a colourless oil, b. p. 82–84°/5 mm. (Found : N, 22.1; S, 24.7. $C_5H_8N_2S$ requires N, 21.8; S, 25.0%).

4-Methyl-2-sulphanilamidomethylthiazole (No. 1423).—4-Methyl-2-aminomethylthiazole (2.5 g.) was heated on the water-bath for $\frac{1}{2}$ hour with a solution of acetylsulphanil chloride (4.7 g.) in anhydrous pyridine (10 c.c.). The mixture was cooled, diluted with water, and the precipitated 4-methyl-2-acetylsulphanilamidomethylthiazole (4.9 g.) collected; this crystallised from aqueous alcohol in cream leaves, m. p. 176° (Found : N, 13.1; S, 19.3. $C_{13}H_{15}O_3N_2S_2$ requires N, 12.9; S, 19.7%).

The foregoing acetamido-compound (4.0 g.) was heated with 2.5N-sodium hydroxide (32 c.c.) at 100° for 1 hour, the solution diluted with water, partly neutralised with acetic acid, the filtered solution (charcoal) acidified with acetic acid, and the precipitate collected. Recrystallisation from aqueous alcohol yielded 4-methyl-2-sulphanilamidomethylthiazole (3.1 g.) in colourless plates, m. p. 124–126° (Found : N, 14.6; S, 23.0. $C_{11}H_{13}O_2N_2S_2$ requires N, 14.8; S, 22.6%).

4-Methyl-2-aminomethylthiazole-5-carboxylic Acid.—A solution of β -benzamidothioacetamide (19.4 g.) in anhydrous methyl alcohol (225 c.c.) and anhydrous pyridine (12 c.c.) was refluxed with ethyl α -chloroacetate (18 c.c.; Dey, J., 1915, 107, 1646) for 5 hours. The solvent was distilled off to incipient crystallisation, and the solution (70 c.c.) chilled, ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate (25 g.; m. p. 140°) separating in long colourless needles; by evaporation of the filtrate a further crop (1.5 g.) was obtained (Found, in recrystallised material, m. p. 140–142° : N, 8.9; S, 10.4. $C_{15}H_{15}O_3N_2S$ requires N, 9.2; S, 10.5%).

A solution of the foregoing benzamido-compound (6.1 g.) in methyl alcohol (50 c.c.) was refluxed with 5N-sodium hydroxide (10 c.c.) for 1 hour. After standing overnight at 20° the alcohol was distilled away at reduced pressure, the residue dissolved in water (70 c.c.), filtered (charcoal), and the solution adjusted to pH 4 with hydrochloric acid; 4-methyl-2-benzamidomethylthiazole-5-carboxylic acid (5.0 g.) separated as a microcrystalline precipitate. The acid crystallised from 50% alcohol in glittering white tablets, m. p. 252–254° (decomp.) (Found : N, 10.3; S, 11.7. $C_{13}H_{13}O_3N_2S$ requires N, 10.2; S, 11.6%).

A solution of crude ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate (15 g.) in methyl alcohol (200 c.c.) was refluxed with 10N-hydrochloric acid (100 c.c.) for 14 hours. The solution was distilled in a current of steam to remove alcohol and benzoic acid and, after the addition of more hydrochloric acid, evaporated to very small volume; on cooling, 4-methyl-2-aminomethylthiazole-5-carboxylic acid hydrochloride separated in small prisms (6 g.), m. p. 248–250° (decomp.) (Found, in material dried at 120°/1 mm. over phosphoric oxide : N, 13.7; Cl, 16.8. $C_6H_8O_2N_2S.HCl$ requires N, 13.5; Cl, 16.9%).

The foregoing hydrochloride (5 g.) was dissolved in water (12 c.c.) and the solution adjusted to pH 3.5—4.0 by addition of 5*N*-sodium hydroxide (ca. 6 c.c.). When the resulting solution was kept on ice, 4-methyl-2-aminomethylthiazole-5-carboxylic acid (2.8 g.) separated in white plates; these crystallised from 50% alcohol in stellate clusters of colourless feathers, m. p. 282—284° (Found: N, 16.4; S, 18.5. $C_5H_8O_3N_2S$ requires N, 16.3; S, 18.6%).

2-Benzamidomethyl-4-thiazolylacetic Acid.—A solution of benzamidomethylthioacetamide (9.7 g.) in anhydrous methyl alcohol (150 c.c.) and anhydrous pyridine (6 c.c.) was refluxed with ethyl γ -bromoacetate (8.5 c.c.; Epprecht, *loc. cit.*) for 4½ hours. The solvent was distilled away at reduced pressure, the residual oil dissolved in warm 1.5*N*-hydrochloric acid (200 c.c.), and the solution filtered (charcoal) and adjusted to pH 7 with dilute sodium hydroxide; ethyl 2-benzamidomethyl-4-thiazolylacetate (12.5 g.) separated, which crystallised from benzene-ligroin in glittering plates, m. p. 86—88° (Found: N, 9.6; S, 10.9. $C_{15}H_{16}O_3N_2S$ requires N, 9.7; S, 11.0%).

A solution of the foregoing crude benzamido-compound (6 g.) in methyl alcohol (60 c.c.) and 5*N*-sodium hydroxide (10 c.c.) was refluxed for 1 hour. The solvent was removed at reduced pressure, the residue dissolved in a small volume of water, and the filtered solution adjusted to pH 4 with hydrochloric acid; 2-benzamidomethyl-4-thiazolylacetic acid (3 g.) separated in colourless plates, which crystallised from dilute alcohol in glittering plates, m. p. 184—186° (Found: N, 10.3; S, 11.6. $C_{13}H_{12}O_3N_2S$ requires N, 10.2; S, 11.6%).

2-Benzamidomethylthiazole-4-carboxylic Acid.—A solution of freshly prepared and redistilled pyruvic acid (75 g.; 60 c.c.) and toluenesulphonic acid (6 g.) in ethyl alcohol (1250 c.c.) and benzene (300 c.c.) was refluxed under a 12" Widmer column with a 10:1 reflux ratio and solvent removed at the rate of 100 c.c./hour. After 5 hours a further quantity of benzene (300 c.c.) was added and the distillation continued for another 4 hours, solvent being removed at the rate of 240—250 c.c./hour. After standing overnight the residual oil was distilled through a 6" Vigreux column, the solvent being removed first at 760 mm. up to 80° to avoid loss of ester; redistillation of the fraction, b. p. 50—65°/20 mm. (75 g.), yielded 68 g. of ethyl pyruvate as a colourless oil, b. p. 54—60°/20 mm. A solution of dry bromine (25 c.c.) in dry carbon tetrachloride (25 c.c.) was added dropwise during ½ hr. to a refluxing solution of ethyl pyruvate (58 g.) in carbon tetrachloride (100 c.c.). After standing for 3 hours, the oil was distilled and yielded a fraction (82 g.), b. p. 96—100°/10 mm., which on redistillation gave ethyl bromopyruvate (70 g.), b. p. 90—94°/8 mm.

A solution of benzamidothioacetamide (9.7 g.) in dioxan (110 c.c.) and benzene (40 c.c.) was heated on the water-bath with ethyl bromopyruvate (8 c.c.) for 2 hours. The solvent was rapidly distilled away at reduced pressure, the residual oil dissolved in 1.7*N*-hydrochloric acid (300 c.c.), and the solution filtered (charcoal), adjusted at 20° with stirring to pH 7.6 by addition of 5*N*-sodium hydroxide, and the precipitate of ethyl 2-benzamidomethylthiazole-4-carboxylate (5.0 g.; m. p. 76—80°) collected. Adjustment of the filtrate to pH 2.8—3.0 with hydrochloric acid effected precipitation of 2-benzamidomethylthiazole-4-carboxylic acid (5.8 g.; m. p. 176—180°). The ester crystallised from benzene-ligroin in colourless plates, m. p. 82—84° (Found: N, 9.7; S, 10.9. $C_{14}H_{14}O_3N_2S$ requires N, 9.7; S, 11.0%); the acid separated from dilute alcohol in glittering colourless leaves, m. p. 180—182° (Found: N, 10.4; S, 11.9. $C_{12}H_{10}O_3N_2S$ requires N, 10.7; S, 12.2%). Interaction of the thioamide and ethyl bromopyruvate in alcoholic solution in the presence of pyridine yielded a dark gum.

Benzamidoacetamidine Hydrochloride.—A mixture of benzamidomethyl cyanide (40 g.), anhydrous chloroform (300 c.c.), and anhydrous ethyl alcohol (59 c.c.) was saturated at 5° with dry hydrogen chloride; the cyanide dissolved as the hydrogen chloride was passed in and then set to a crystalline mass which redissolved as the solution became saturated. After standing at 4° for 16—20 hours, the chloroform was pumped off at room temperature, and the crystalline residue (53 g.; m. p. 144—146°) of benzamidoacetiminooether hydrochloride, containing ammonium chloride as impurity, was washed with a little dry chloroform and dried in a vacuum (Found: N, 12.2; Cl, 15.8. $C_{11}H_{14}O_2N_2.HCl$ requires N, 11.5; Cl, 14.6%). This was added to alcohol (300 c.c.; lime-dried), which had been previously saturated with dry ammonia at 5°, and the mixture swirled at room temperature until solution was obtained and then allowed to stand in a closed vessel at ca. 4° for 24 hours. After addition of absolute ether (200 c.c.), the crystalline precipitate of benzamidoacetamidine hydrochloride (44 g.), m. p. 184—186°, was collected and dried in a vacuum over sulphuric acid; from alcohol-ether a sample separated in colourless nacreous plates, m. p. 187° (Found: N, 20.1; Cl, 17.1. $C_9H_{11}ON_3.HCl$ requires N, 19.7; Cl, 16.6%). The free amidine, m. p. 132—134°, precipitated by the addition of 5*N*-sodium hydroxide to a cold 20% aqueous solution of the hydrochloride, was unstable and rapidly became converted into benzamidoacetamide, which crystallised from boiling water in large colourless prisms, m. p. 186° (Found: C, 60.8; H, 5.8; N, 16.1. Calc. for $C_9H_{10}O_2N_2$: C, 60.6; H, 5.7; N, 15.7%).

4:6-Dimethyl-2-benzamidomethylpyrimidine.—A solution of benzamidoacetamidine hydrochloride (30 g.) in alcohol (150 c.c.) was refluxed with anhydrous potassium carbonate (20 g.) and acetylacetone (18 g.) for 4 hours. The alcohol was distilled off, water added to the residue, and the precipitated oil, which slowly solidified to a dark gum, lixiviated with warm dilute hydrochloric acid and, after chilling, the insoluble benzamidoacetamide removed. Basification of the filtrate with 5*N*-sodium hydroxide precipitated 4:6-dimethyl-2-benzamidomethylpyrimidine (8.7 g.; m. p. 192—194°), which crystallised from aqueous methyl alcohol (charcoal) in slender colourless needles, m. p. 200° (Found: C, 69.6; H, 6.3; N, 17.8. $C_{14}H_{15}ON_3$ requires C, 69.7; H, 6.3; N, 17.4%). Many modifications of the above procedure failed to increase the yield.

4:6-Dimethyl-2-aminomethylpyrimidine.—A solution of crude 4:6-dimethyl-2-benzamidopyrimidine (36.5 g.) in 5*N*-hydrochloric acid (225 c.c.) was refluxed for 4 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to dryness under reduced pressure. The residual hydrochloride was dissolved in warm water (200 c.c.), filtered (charcoal), evaporated under reduced pressure to small volume (100 c.c.), chilled, and strongly basified with 5*N*-sodium hydroxide. After standing, the precipitate was collected (22 g.; m. p. 152—156°), drained, boiled with water (250 c.c.), the unchanged benzamido-compound (4.0 g.) removed, and the filtered solution allowed to cool; 4:6-dimethyl-2-aminomethylpyrimidine (17 g.) separated in colourless, hydrated, felted needles which on drying at 100° yielded an

anhydrous white powder, m. p. 168° (Found: C, 61.4; H, 8.1; N, 30.9. $C_7H_{11}N_3$ requires C, 61.3; H, 8.1; N, 30.6%). The monohydrochloride separated from methyl alcohol-ether in slender white needles, m. p. 244–246° (Found: N, 24.3. $C_7H_{11}N_3 \cdot HCl$ requires N, 24.2%).

Acetylsulphanilamidoacetamidine Hydrochloride.—A mixture of acetylsulphanilamidomethyl cyanide (14.6 g.), dry chloroform (100 c.c.), and absolute ethyl alcohol (13.7 c.c.) was saturated with dry hydrogen chloride at 5° and then kept at ca. 4° for 7 days with occasional shaking. The solvents were pumped off at room temperature, the residue mixed with anhydrous alcohol (100 c.c.) which had previously been saturated with dry ammonia, and the solution, which rapidly crystallised, allowed to stand at room temperature for 16 hours. The solvent was pumped off, and the crystalline residue (16 g.; m. p. 160°) of acetylsulphanilamidoacetamidine hydrochloride washed with ether. For analysis a sample was recrystallised from alcohol-ether and obtained in white needles, m. p. 164–166° (Found: N, 19.0; Cl, 12.0. $C_{10}H_{14}O_3N_4S \cdot HCl$ requires N, 18.5; Cl, 11.8%). The free amidine was precipitated from the concentrated aqueous solution of the hydrochloride by 5N-sodium hydroxide but rapidly decomposed to acetylsulphanilamidoacetamide, which crystallised from boiling water in colourless rectangular prisms, m. p. 218–220° (Found: C, 44.1; H, 5.0; N, 16.0. $C_{10}H_{13}O_3N_3S$ requires C, 44.2; H, 4.8; N, 15.9%).

4:6-Dimethyl-2-sulphanilamidomethylpyrimidine (No. 1427).—Acetylsulphanilamidoacetamidine hydrochloride (10 g.), acetylacetone (6.0 c.c.), pyridine (14 c.c.), and water (6 c.c.) were heated together at 100° for 4 hours. Water (20 c.c.) was added, and the precipitate (4.8 g.; m. p. 256°) collected and recrystallised from aqueous alcohol, 4:6-dimethyl-2-acetylsulphanilamidomethylpyrimidine being obtained in slender cream needles, m. p. 260–262° (Found: C, 53.7; H, 5.3; N, 17.2. $C_{15}H_{18}O_3N_4S$ requires C, 53.9; H, 5.4; N, 16.9%).

The foregoing acetamido-compound (7.8 g.) was dissolved in 2.5N-sodium hydroxide (62 c.c.), and the solution heated on the water-bath for 1 hour, cooled, partly neutralised with dilute hydrochloric acid, and filtered (charcoal). Adjustment of the filtrate to pH 7.0 effected separation of 4:6-dimethyl-2-sulphanilamidomethylpyrimidine (6.6 g.) in microscopic needles, m. p. 230–232°, which after a further crystallisation from aqueous alcohol had m. p. 232–234° (Found: N, 19.4; S, 11.0. $C_{15}H_{18}O_3N_4S$ requires N, 19.2; S, 10.6%).

The compound was also obtained by the following route. Acetylsulphanil chloride (3 g.) was added to a solution of 4:6-dimethyl-2-aminomethylpyrimidine (2 g.) and sodium hydrogen carbonate (2 g.) in 60% acetone (50 c.c.). After being warmed on the water-bath for a short time, the mixture was diluted with water, and the precipitate collected. Crystallisation from aqueous alcohol yielded 4:6-dimethyl-2-acetylsulphanilamidomethylpyrimidine in cream needles, m. p. 261–262°, alone and in admixture with a sample prepared as above described.

Condensation of Benzamidoacetamidine with Malononitrile: 1-Amino-2-benzamidoethylidenemalononitrile.—A solution of benzamidoacetamidine hydrochloride (21.3 g.) in anhydrous alcohol (150 c.c.) was converted into the free amidine base by addition of a solution of sodium (2.3 g.) in alcohol (50 c.c.). Malononitrile (7.5 c.c.) was added, and the solution allowed to stand at 40–45°; the mixture rapidly turned orange and in 2 hours developed an ammoniacal odour and began depositing crystals. After 48 hours at this temperature the mixture was chilled, and the crystalline, almost colourless precipitate of 1-amino-2-benzamidoethylidenemalononitrile (25.5 g.; m. p. 206°) collected. A sample crystallised from dilute alcohol in colourless, glistening leaves, m. p. 220–222° (decomp.) with softening at 210° (Found, in material dried at 80°/2 mm. over phosphoric oxide: C, 63.6; H, 4.5; N, 24.9, 25.0. $C_{15}H_{10}ON_4$ requires C, 63.8; H, 4.4; N, 24.8%).

Condensation of Benzamidoacetamidine with Ethyl Cyanoacetate: Ethyl 1-Amino-2-benzamidoethylidenecyanoacetate.—A mixture of ethyl cyanoacetate (12.4 g.) and an anhydrous alcoholic solution of benzamidoacetamidine (prepared as in the foregoing example from 21.3 g. of benzamidoacetamidine hydrochloride in 150 c.c. alcohol and 2.3 g. of sodium in 50 c.c. alcohol) was kept for 48 hours at 40°; crystals rapidly separated with development of an ammoniacal odour. The mixture was chilled, and the crystalline precipitate of ethyl 1-amino-2-benzamidoethylidenecyanoacetate (24 g.; m. p. 196°) collected. A sample separated from dilute alcohol in colourless felted leaves, m. p. 198–200° (Found: C, 61.3; H, 5.4; N, 15.6, 15.5. $C_{14}H_{13}O_3N_3$ requires C, 61.5; H, 5.5; N, 15.4%).

α -Benzamidothiopropionamide.— α -Benzamidopropionitrile (11.2 g.) was added to freshly prepared methanolic ammonium sulphide (obtained by dissolution of 6 g. of ammonia and then 6 g. of hydrogen sulphide in 75 c.c. of methyl alcohol) and the solution kept in a sealed bottle at room temperature for 16 hours. On dilution with water α -benzamidothiopropionamide (7.6 g.) slowly separated; this crystallised from aqueous methyl alcohol in colourless needles, m. p. 146° (Found: N, 13.8; S, 15.4. $C_{10}H_{12}ON_2S$ requires N, 13.5; S, 15.4%).

4-Methyl-2-(1'-aminoethyl)thiazole.—A solution of the foregoing amide (50 g.) in methyl alcohol (200 c.c.) and pyridine (38 c.c.) was refluxed with chloroacetone (24 c.c.) for 2 hours, and the alcohol then distilled off. Addition of water to the residue precipitated 4-methyl-2-(1'-benzamidoethyl)thiazole (50 g.), which crystallised from aqueous methyl alcohol in colourless needles, m. p. 112° (Found: N, 11.6; S, 13.4. $C_{13}H_{14}ON_2S$ requires N, 11.4; S, 13.0%).

A solution of the foregoing crude compound (50 g.) in 5N-hydrochloric acid (400 c.c.) was refluxed for 7 hours, cooled, the benzoic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Water (300 c.c.) was added, and the solution evaporated to very small volume, cooled, strongly basified with 10N-sodium hydroxide, and extracted with chloroform (2 \times 50 c.c.). After drying and distillation, the chloroform extracts yielded 4-methyl-2-(1'-aminoethyl)thiazole as a colourless oil (21 g.), b. p. 98–100°/12 mm. (Found: N, 20.0; S, 22.5. $C_6H_{10}N_2S$ requires N, 19.7; S, 22.6%).

α -Acetylsulphanilamidothiopropanamide.— α -Acetylsulphanilamidopropionitrile (9.2 g.) was added to freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 5 g. of hydrogen sulphide in 100 c.c. of methyl alcohol), and the mixture kept at 20° with frequent shaking for 24 hours. Addition of water (150 c.c.) caused the thio-amide (6.6 g.) slowly to separate in colourless prisms, m. p. 220; these crystallised from aqueous methyl alcohol in stout prisms, m. p. 226° (Found: N, 14.2; S, 21.1. $C_{11}H_{14}O_3N_2S_2$ requires N, 14.0; S, 21.3%).

4-Methyl-2-(1'-sulphanilamidoethyl)thiazole (No. 1424).—A solution of the foregoing amide (5.0 g.) in

alcohol (50 c.c.), water (5 c.c.), and pyridine (4 c.c.) was refluxed with chloroacetone (2.4 g.) for 2 hours, and the alcohol then distilled off. Addition of water (50 c.c.) precipitated 4-methyl-2-(1'-acetylsulphanilamidoethyl)thiazole (5.2 g.; m. p. 172°) which crystallised from aqueous alcohol in pale cream needles, m. p. 180—182° (Found: N, 12.3; S, 18.6. $C_{14}H_{17}O_2N_3S_2$ requires N, 12.4; S, 18.9%).

Hydrolysis of the foregoing compound (4.2 g.) with 2.5N-sodium hydroxide at 100° for 1 hour yielded 4-methyl-2-(1'-sulphanilamidoethyl)thiazole (2.4 g.), which separated from dilute alcohol in colourless prisms, m. p. 168° (Found: N, 14.5; S, 21.3. $C_{13}H_{15}O_2N_3S_2$ requires N, 14.2; S, 21.6%).

β -Benzamidothiopropionamide.—A solution of β -benzamidothiopropionitrile (42 g.) in 96% alcohol (325 c.c.) containing 3.3% w/w ammonia was saturated with hydrogen sulphide and kept at ca. 40° for 5 days, more hydrogen sulphide being added each day. Solvent was pumped off from the semi-solid mixture, ether in excess added, and the precipitate collected. This was dissolved in 90% methyl alcohol (500 c.c.), the sulphur removed, and the filtrate evaporated to incipient crystallisation (vol. 250 c.c.); on standing in the ice chest, β -benzamidothiopropionamide (30 g.) separated in glittering colourless rhombs, m. p. 160—162°. A further quantity of less pure material was separated from the mother-liquor (Found: N, 13.6; S, 15.2. $C_{10}H_{13}ON_2S$ requires N, 13.5; S, 15.2%). The compound was obtained in similar yield by saturating the cold methyl-alcoholic solution of the nitrile with ammonia and then with hydrogen sulphide and keeping it in a sealed vessel at 40° for 5 days.

4-Methyl-2-(2'-benzamidoethyl)thiazole.—A solution of the foregoing amide (41.6 g.) in anhydrous methyl alcohol (600 c.c.) was refluxed with chloroacetone (24 c.c.) and anhydrous pyridine (32 c.c.) for 4½ hours. After standing overnight the solvent was distilled off, and the oil which separated dissolved in warm N-hydrochloric acid (300 c.c.), the solution filtered (charcoal), and the filtrate adjusted to pH 7.0 with ammonia; 4-methyl-2-(2'-benzamidoethyl)thiazole (40 g.) separated as an oil which solidified on scratching and freezing. The compound was obtained in slender colourless needles, m. p. 74—76°, by dissolution in warm benzene-ligroin and allowing the solvent to evaporate slowly in a current of cold filtered air (Found: C, 64.0; H, 5.9; N, 11.8; S, 13.6. $C_{13}H_{14}ON_2S$ requires C, 63.5; H, 5.7; N, 11.4; S, 13.0%).

4-Methyl-2-(2'-aminoethyl)thiazole.—The foregoing crude benzamido-compound (32 g.) was refluxed for 4 hours with 5N-hydrochloric acid (260 c.c.), the solution chilled, and the precipitated benzoic acid removed. The filtrate was evaporated to small volume, chilled, strongly basified with 10N-sodium hydroxide, and extracted several times with ether; the ethereal solution after drying over potassium carbonate yielded 4-methyl-2-(2'-aminoethyl)thiazole (15 g.) as a colourless oil, b. p. 102—104°/10 mm. (Found: N, 19.8; S, 22.2. $C_8H_{10}N_2S$ requires N, 19.7; S, 22.5%).

4-Methyl-2-(2'-sulphanilamidoethyl)thiazole (No. 1323).—A solution of acetylsulphanil chloride (17 g.) in acetone (50 c.c.) was added dropwise during 45 minutes to a mixture of 4-methyl-2-(2'-aminoethyl)thiazole (10 g.), sodium hydrogen carbonate (10 g.), water (150 c.c.), and acetone (20 c.c.) stirred at 10—15°. Stirring was continued at 20° for a further 4 hours, water (150 c.c.) added, and the precipitate of 4-methyl-2-(2'-acetylsulphanilamidoethyl)thiazole (26 g.; m. p. 110°) collected and washed with water. The compound is insoluble in cold water but easily soluble in cold dilute hydrochloric acid and dilute sodium hydroxide. A sample crystallised from dilute alcohol in colourless needles, m. p. 116—118° (Found, in material dried at 1 mm. over phosphoric oxide: N, 12.3; S, 18.7. $C_{14}H_{17}O_2N_3S_2$ requires N, 12.4; S, 18.9%).

A solution of the foregoing crude acetamido-compound (20 g.) in 2.5N-sodium hydroxide (200 c.c.) was heated on the water-bath for 75 minutes. 10N-Hydrochloric acid (70 c.c.) was added, the solution filtered (charcoal), cooled, and adjusted with simultaneous scratching to pH 6.6—7.0 with dilute sodium hydroxide; 4-methyl-2-(2'-sulphanilamidoethyl)thiazole separated in small colourless crystals (15.8 g.; m. p. 92°), which crystallised from dilute methyl alcohol in elongated needles, m. p. 98—100° (Found, in material dried over phosphoric oxide at 1 mm.: N, 14.4; S, 21.4. $C_{12}H_{15}O_2N_3S_2$ requires N, 14.2; S, 21.6%). The compound is considerably more soluble in cold 5% lactic acid than is sulphathiazole.

β -Benzamidothiopropionamide Hydrochloride.—A solution of β -benzamidothiopropionitrile (35 g.) in anhydrous chloroform (300 c.c.) and anhydrous ethyl alcohol (46 c.c.) was saturated at 5° with dry hydrogen chloride and set aside for 18—24 hours at 0—4°. The solvent was completely pumped off at 20°, and the glittering crystalline residue of β -benzamidothiopropionimino-ether hydrochloride was mixed with cold anhydrous ethyl alcohol (400 c.c.) and saturated with dry ammonia at 5°. The clear solution which resulted was allowed to stand at 5° for 24—30 hours, the ammonia pumped off at 20°, the volume made up to 400 c.c. with lime-dried alcohol, and the solution filtered at the b. p. to remove ammonium chloride and kept on ice; β -benzamidothiopropionamide hydrochloride separated in large colourless transparent cubes (34 g.; m. p. 174—180°) which were collected and dried in a vacuum. From the mother-liquors a further 7 g. (m. p. 178—180°) was obtained by evaporation. A sample recrystallised from anhydrous ethyl alcohol had m. p. 178—180° (Found: N, 18.4; Cl, 16.4. $C_{10}H_{14}ON_2Cl$ requires N, 18.4; Cl, 15.6%).

All attempts to condense this amidine with acetylacetone (i) in dilute alcohol in presence of sodium carbonate at the b. p., (ii) in refluxing anhydrous alcohol in presence of sodium carbonate, (iii) in warm (40°) and in refluxing anhydrous alcohol in presence of 1 mol. or 2 mols. of sodium ethoxide failed to yield any of the required pyrimidine. In (i) a quantitative yield of β -benzamidothiopropionamide was obtained which crystallised from boiling water in heavy colourless prisms, m. p. 174—176° (Found: C, 62.2; H, 6.3; N, 14.6. $C_{10}H_{13}O_2N_3$ requires C, 62.6; H, 6.3; N, 14.6%).

γ -Phthalimidothiobutyramide.—A mixture of 3-phthalimidopropyl cyanide (20 g.) and freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 12 g. of hydrogen sulphide in 120 c.c. of methyl alcohol) was kept at 40° in a closed vessel with frequent shaking for 48 hours. The mixture was chilled, and the precipitated amide (11.5 g.; m. p. 184°) collected; on re-heating the filtrate to 40—45° for 5 days, a further quantity (2 g.) separated. For analysis a sample was recrystallised from alcohol and obtained in colourless needles, m. p. 186° (Found: N, 11.3; S, 13.2. $C_{12}H_{13}O_2N_3S$ requires N, 11.3; S, 12.9%).

4-Methyl-2-(3'-aminoethyl)thiazole.—The above amide (10 g.), chloroacetone (5.6 g.), pyridine (6.5 c.c.), and methyl alcohol (70 c.c.) were refluxed together for 2 hours, the solvent distilled off, and the residue diluted with water. The oil which separated slowly solidified to a crystalline mass (11.2 g.) of

4-methyl-2-(3'-phthalimidopropyl)thiazole, which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 80° (Found: N, 10.0; S, 11.4. $C_{14}H_{14}O_2N_2S$ requires N, 9.8; S, 11.2%).

The foregoing compound (45 g.) was refluxed with 10N-hydrochloric acid (340 c.c.) for 8 hours, the mixture chilled, the phthalic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Basification of the residue with 10N-sodium hydroxide and extraction with chloroform yielded 4-methyl-2-(3'-aminopropyl)thiazole, which distilled as a colourless oil (19.5 g.), b. p. 120–122°/12 mm. (Found, in redistilled sample: N, 17.8; S, 21.2. $C_7H_{12}N_2S$ requires N, 17.9; S, 20.5%).

4-Methyl-2-(3'-sulphanilamidopropyl)thiazole (No. 1432).—Acetylsulphanilyl chloride (5 g.) was added to a rapidly stirred solution of 4-methyl-2-(3'-aminopropyl)thiazole (3 g.) and sodium hydrogen carbonate (3 g.) in 50% aqueous acetone (25 c.c.), and the mixture stirred for $\frac{1}{2}$ hour at room temperature and then for a further $\frac{1}{2}$ hour at 50–60°. Addition of water precipitated 4-methyl-2-(3'-acetylsulphanilamidopropyl)thiazole (6.2 g.), which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 91° (Found: N, 11.8; S, 17.3. $C_{14}H_{18}O_2N_2S_2$ requires N, 11.9; S, 16.9%). Deacetylation with 2.5N-sodium hydroxide at 100° for 1 hour yielded 4-methyl-2-(3'-sulphanilamidopropyl)thiazole, which separated from aqueous methyl alcohol in colourless needles, m. p. 130–132° (Found: N, 13.8; S, 20.5. $C_{13}H_{17}O_2N_2S_2$ requires N, 13.5; S, 20.6%).

γ -Phthalimidobutyramidine Hydrochloride.—A solution of 3-phthalimidopropyl cyanide (20 g.) in dry chloroform (100 c.c.) and anhydrous alcohol (22 c.c.) was saturated at 5° with dry hydrogen chloride and kept overnight at 5°. The solvent was completely removed at 30° under reduced pressure, anhydrous alcohol (120 c.c.) added, and the solution saturated at 5° with dry ammonia. After standing at 0–5° for 72 hours, the solvent and excess ammonia were distilled away at < 30°; crystallisation of the residue from a small volume of water yielded γ -phthalimidobutyramidine hydrochloride (12 g.) in colourless nacreous plates, m. p. 180–182°; for analysis a sample was recrystallised from alcohol-ether and obtained in colourless plates, m. p. 186° (Found: N, 16.1; Cl, 14.0. $C_{12}H_{13}O_2N_3HCl$ requires N, 15.7; Cl, 13.3%). Attempts to condense this compound with acetylacetone failed to yield any of the desired pyrimidine.

5-Benzamidothiohexoamide.—A solution of 5-benzamido-*n*-amyl cyanide (4 g.) in methyl alcohol (24 c.c.) was saturated with ammonia and then with hydrogen sulphide at 0° and kept in a closed vessel at 50° for 72 hours. Addition of a small amount of water effected separation of the hexoamide (1.25 g.; m. p. 90°), which crystallised from aqueous methyl alcohol in colourless leaves, m. p. 94–96° (Found: N, 11.4; S, 12.4. $C_{11}H_{19}ON_2S$ requires N, 11.2; S, 12.8%).

Use of ethanolamine or of sodium or potassium ethoxide as catalyst failed to improve the yield, and accordingly the attempt to prepare the corresponding thiazole derivative was abandoned.

5-Benzamido-*n*-hexoamide Hydrochloride.—A solution of 5-benzamido-*n*-amyl cyanide (10 g.) in chloroform (60 c.c.) and ethyl alcohol (10 c.c.) was saturated at 5° with dry hydrogen chloride, kept at 5° for 24 hours, and evaporated to dryness at ca. 20°, and anhydrous alcohol (50 c.c.), which had previously been saturated at 0° with ammonia, was added. After standing at 5° for 72 hours and then for a further 24 hours at room temperature, a portion of the alcohol was distilled off at reduced pressure, and the residue diluted with dry ether. The oil which separated slowly solidified to a crystalline mass of the hydrochloride (11.5 g.; m. p. 130°); crystallisation from alcohol-ether yielded white prisms, m. p. 132° (Found: N, 15.1; Cl, 13.7. $C_{13}H_{19}ON_2HCl$ requires N, 15.6; Cl, 13.2%). All attempts to obtain a pyrimidine derivative by condensation with acetylacetone were unsuccessful.

11-Benzamidothioundecoamide.—Hydrogen sulphide was passed into a solution of 10-benzamido-decyl cyanide (25 g.) in methyl alcohol (125 c.c.) and aqueous ammonia (*d* 0.880; 20 c.c.) until an increase in weight of 10 g. was obtained. The solution was heated in a closed vessel for 7 days at 35°, water (100 c.c.) added, and the precipitate collected and recrystallised from aqueous methyl alcohol, 11-benzamidothioundecoamide (10.5 g.) separating in pale cream needles, m. p. 112° (Found: N, 8.9; S, 10.0. $C_{18}H_{29}ON_2S$ requires N, 8.7; S, 10.0%).

4-Methyl-2-(ω -aminodecyl)thiazole.—A solution of the foregoing amide (10.5 g.) in methyl alcohol (75 c.c.) and pyridine (5.4 c.c.) was refluxed with chloroacetone (4.0 c.c.) for 3 hours. The excess of solvent was distilled off, water (100 c.c.) added to the residue, and the 4-methyl-2-(ω -benzamido-decyl)thiazole (11.5 g.; m. p. 54°) collected; this recrystallised from aqueous methyl alcohol in white plates, m. p. 58–60° (Found: C, 70.1; H, 8.5; N, 7.8; S, 8.6. $C_{21}H_{39}ON_2S$ requires C, 70.4; H, 8.4; N, 7.8; S, 9.0%).

The foregoing crude benzamido-compound (27.3 g.) was refluxed with 10N-hydrochloric acid (273 c.c.) for 12 hours, the mixture chilled, and the benzoic acid filtered off. The filtrate was evaporated to small volume at reduced pressure, diluted with water (200 c.c.), and evaporated to dryness. Addition of 5N-sodium hydroxide to the residue, followed by chloroform extraction and distillation, yielded 4-methyl-2-(ω -aminodecyl)thiazole as a pale yellow oil (10 g.), b. p. 166–170°/0.5 mm. (Found: N, 11.0; S, 12.8. $C_{14}H_{28}N_2S$ requires N, 11.0; S, 12.6%).

4-Methyl-2-(ω -sulphanilamidodecyl)thiazole (No. 1433).—Acetylsulphanilyl chloride (3.2 g.) was added to a stirred mixture of the foregoing base (3.0 g.), sodium hydrogen carbonate (2.0 g.), and 50% aqueous acetone (20 c.c.). After being stirred for $\frac{1}{2}$ hour at room temperature, the mixture was heated on the water-bath for $\frac{1}{2}$ hour, diluted with water (100 c.c.), and the precipitate (5.2 g.; m. p. 102°) collected. Recrystallisation from aqueous methyl alcohol yielded 4-methyl-2-(ω -acetylsulphanilamidodecyl)thiazole in white needles, m. p. 102–104° (Found: N, 8.9; S, 14.2. $C_{22}H_{35}O_2N_2S_2$ requires N, 9.3; S, 14.2%). Deacetylation with 2.5N-sodium hydroxide in 50% aqueous alcohol at the reflux for 1½ hours gave 4-methyl-2-(ω -sulphanilamidodecyl)thiazole, which separated from aqueous methyl alcohol in pale cream prisms, m. p. 108° (Found: N, 10.4; S, 15.8. $C_{20}H_{31}O_2N_2S_2$ requires N, 10.3; S, 15.7%).

The authors thank Mr. H. S. Jefferies, B.Sc., for carrying out the biological tests, Mr. D. Fairbairn for technical assistance, and Mr. N. Virgo for the analyses.

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[Received, November 25th, 1946.]

256. Application of Thallium Compounds in Organic Chemistry. Part XI.*

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A summary is given of earlier work on the thallium method of alkylating sugars and its more recent extensions. It is pointed out that entry of thallium into carbohydrate molecules, controlled by Purves by varying the sizes of the molecules carrying the ethoxide in solution, can also be controlled by varying the effective size of the thallium atom by anchoring it by attached alkyl groups. A case of methylation by boiling a diethylthallium derivative with methyl iodide is also described.

ALKYLATIONS by reaction between thallous compounds and alkyl iodides were first described by Fear and Menzies (*J.*, 1926, 937), *o*-methoxybenzaldehyde, dimethyl hydroxymethoxy-succinate, and a mixture of trimethyl methylglucosides being obtained from thallous salicylaldehyde, tetrathallium tartrate, and trithallium methylglucoside. Twelve years later Purves and Hudson (*J. Amer. Chem. Soc.*, 1937, 59, 49) methylated by this method α -methyl- and α -benzyl-fructofuranosides, both obtained by them from the uncrystallised mixture of isomeric methylfructofuranosides first prepared by the author (*J.*, 1922, 121, 2238). Later, Hirst, Jones, and others (*J.*, 1938, 497; 1939, 458, 1482, 1867, 1884; 1942, 76; 1946, 506) described the thallation and initial methylation of an arabo-pectic acid complex and a number of vegetable gums, thus altering their solubilities so that methylation could be completed by Purdie's reaction. Hirst and Jones also showed (*J.*, 1938, 1695) that the action of methyl iodide on trithallium methylglucoside gave a mixture of 50% of 2 : 4 : 6-, 36% of 2 : 3 : 6-, 10% of 3 : 4 : 6-, and 4% of 2 : 3 : 4-trimethyl methylglucosides, so that positions 2, 3, 4, and 6 were methylated in 90, 50, 64, and 96% respectively of the whole product, positions 2 and 6 being methylated simultaneously in 86%, but positions 3 and 4 were only methylated together to the extent of 14%.

Purves later (*J. Amer. Chem. Soc.*, 1944, 66, 59) investigated the distribution of amorphous and crystalline material in cellulose by treating it with thallous ethoxide dissolved in organic solvents of different molecular sizes.

Thallation followed by treatment with methyl iodide thus affords a method of initial partial methylation capable of being used in non-aqueous solvents, occasionally applicable where sodium hydroxide and methyl sulphate are ineffectual. Purves and Hudson's preparation of dimethyl methyl- and benzyl-fructosides and Hirst and Jones's preparation of partly methylated methylglucosides indicate that thallation can be controlled and used in the preparation of partly methylated sugars.

These authors have laid stress on results rather than on experimental methods. A recapitulation and extension of published and unpublished observations on the thallous derivatives of some of the more simple sugars and allied substances may therefore be of use.

Treatment of substances containing carboxyl or hydroxyl groups with aqueous thallous hydroxide generally results in replacement of the labile hydrogen by the metal. Where hydroxyl hydrogen is replaced, the metal can be accurately titrated with standard acid; it is also converted into thallous carbonate by passing carbon dioxide through the solution. The first compound described in which both replacements occur in the same molecule was tetrathallium tartrate (Part II). Hexathallium gluconate in which five of the six metallic atoms can be titrated was described in Part IV. *Tetrathallium mesotartrate*, *dithallium glycollate*, and *dithallium lactate* are described below. *Trithallium glycerol* and *tetrathallium erythritol* are both sparingly soluble, separating slowly on mixing solutions of the parent compound with aqueous thallous hydroxide. Hexathallium sorbitol was described in Part IV. Many of these and other thallium compounds crystallise well (cf. *Nature*, 1931, 907) so the recognisable patterns formed by mixing drops of the reacting solutions or on allowing their hot solutions to cool on a microscope slide are suitable for identification purposes. So far as is known all hydroxyl hydrogen atoms in straight-chain compounds can be substituted by the metal. When, however, the compound contains a pyranose, furanose, or an attached benzene ring, substitution may be incomplete. For instance, methylarabinoside (Part IV) gives a trithallium derivative, but so, under similar conditions, does methylglucoside (Part III). Sucrose, with eight hydroxyl groups, and salicin, with five, give *tetrathallium sucrose* and *trithallium salicin*. It is only in

* Previous parts of this series published in the *Journal* are : I, 1924, 125, 1148; II, 1925, 127, 2369; III, 1926, 937; IV, 1928, 186; V, 1930, 1571; VI, 1931, 2239; VII, 1932, 2604; VIII, 1932, 2734; IX, 1933, 21; X, 1936, 1678.

rings containing an oxygen atom that incomplete thallation has been observed. Inositol, in which all six hydroxyl groups are secondary, forms sparingly soluble *hexathallium inositol*.

Replacement of hydrogen by the metal in certain cases is thus incomplete. Incomplete also may be subsequent replacement of the metal on treatment with methyl iodide. The attempted methylation of tetrathallium tartrate gave, for instance, after 100 hours, a syrup whose methoxyl content indicated that only three of the metallic atoms had reacted (Part III).

The isolation of well-defined thallous derivatives recalls McKenzie's suggestion (*J.*, 1899, **75**, 765) that a possible explanation of methylation by the silver oxide method is the intermediate formation of an unstable silver derivative which subsequently undergoes double decomposition with the alkyl halide (see also Lander, *J.*, 1900, **77**, 747; 1903, **83**, 416); but these intermediate compounds have never been isolated. Many of the thallous compounds are somewhat unstable, but the fact that they can be isolated facilitates more detailed examination of the mechanism of methylation. Both the occasional incomplete thallation and the usual incomplete subsequent methylation are probably partly due to steric hindrance, but this cause does not act alone. There are also to be considered the alkalinity of the metal or organo-metallic group, the dissociation constant of each individual labile hydrogen, the co-ordinating capacity of the metal, and the presence or absence of water, small amounts being occasionally of importance. Information on the above, and reciprocally, on the properties of the sugars, can be obtained by considering the courses of different methods of substitution on the same, and of the same method on different, hydroxyl compounds.

Steric hindrance certainly plays a part. Purves, for instance, has shown that the depth of entry of thallous ethoxide into fibres of cellulose depends, in the case of the ethers, on the lengths of the carbon chains attached to the oxygen of the ethers. Maxted (*J.*, 1937, 1004) showed that the catalytic activity of platinum in hydrogenations is inhibited by alkyl sulphides in proportion to the lengths of the carbon chains attached to the sulphur. The alkyl groups act like umbrellas. Similar protection of derivatives of β -diketones from hydrolysis, increasing with the length of the alkyl groups attached to the metal, was described in Part X (*loc. cit.*, p. 1880). The probable similar mechanism in this case also is made clear by Powell and Crowfoot's observation (*Z. Krist.*, 1934, **87**, 370) that the alkyl groups in the dialkylthallous compounds are attached at an angle of 180° . The effective size of the thallous atom may thus be increased in a known way without destroying, but not without altering, its power of replacing labile hydrogen, Berry, Lowry, and Gilbert (*J.*, 1928, 1761) having shown that the dialkylthallonium ions are derived from relatively weak bases. One dialkylthallium group probably does not differ much from another in basicity, so that differences between homologous organometallic derivatives may be mainly of steric origin. The non-alkylated metal, however, is a stronger base. It is shown below that in alkaline solutions, where all four labile hydrogen atoms of tartaric acid are replaced by the metal, only three are replaced by the dialkylthallium group. This difference is probably due to both the two causes indicated above. Both causes are also probably concerned in Brady and Hughes's results. They described both mono- and di-thalliumdiphenol, but only mono(diethylthallium)diphenol (*J.*, 1933, 1228). Whatever the cause and whatever alkylation method be used, it is always the insertion of the last group that is the most difficult. Even the silver oxide method occasionally breaks down. Purdie and Young, for instance (*J.*, 1910, **97**, 1524), found that the 3 : 4-dimethyl ether of 2 : 5-dimethylhexane-2 : 3 : 4 : 5-tetraol resisted methylation in this way. McKenzie and Wren (*J.*, 1910, **97**, 473) could only methylate the secondary hydroxyl group of triphenylethylene glycol by its means. Other methods break down more easily. Both the methyl sulphate (Haworth, *J.*, 1915, **107**, 15) and the thallium method (Part III) give incomplete methylation when applied to tartaric acid; and Schlubach and Firgau (*Ber.*, 1926, **59**, 2100) found that, although the potassium salt of 2 : 3 : 6-trimethyl β -methylglucoside gave an 86% yield of tetramethyl β -methylglucoside on treatment with methyl iodide, yet it was unaffected by propyl iodide, benzyl chloride, or acetobromoglucose. The smaller the metal atom or the entering group, and the looser the structure of the metallic derivative, as in Hirst and Jones's preparations of partly methylated methylglucosides and methylarabinosides referred to above, or in Percival's preparation of acetylated trimethyl sucrose (*J.*, 1935, 648), the more likely is substitution of the metal to be complete.

With regard to the varying dissociation of hydrogen from one sugar to another, it is difficult to explain that while the thallation of hexahydroxy-alcohols takes place instantly, that of glycerol and of erythritol takes hours, the solubilities of the resulting thallated derivatives being of the same order, on any other ground than that the lower alcohols must have smaller dissociation constants.

It will also be recalled that the silver oxide method began from following up Purdie and

Pitkeathly's observation (*J.*, 1899, **75**, 153) that in the course of preparation of esters by the action of alkyl halides on silver salts certain anomalous results were encountered, the tartaric esters obtained having abnormally high rotations, and it was ascertained that alkoxy-derivatives were produced during the reaction; *i.e.*, the substitution of silver, known to have a high capacity for forming co-ordination compounds, took place not only on the acid but also on the neighbouring hydroxyl group. This makes it difficult to believe, without further proof, that the replacement of thallium, also a readily co-ordinating element, by other groups always takes place on the same oxygen atom as that to which the metal was attached before reaction with the alkylating agent.

The incomplete thallation referred to above varies in some cases with quite small differences in the conditions of preparation, so that exact repetition of analytical results is occasionally difficult. This difficulty was encountered by Assat, Haas, and Purves (*J. Amer. Chem. Soc.*, 1944, **66**, 61). It is also met with in the analyses of derivatives of sucrose and cellulose and in those of ethylene glycol and of pentaerythritol. In the last two cases the solubility of the derivatives is of the same order as that of thallous hydroxide, and the analyses suggest that both the derivatives of the polyhydric primary alcohols and thallous hydroxide crystallise together. It is important to make clear that these analytical inexactitudes are due, not to the difficulty of determining the metal or of determining carbon or hydrogen in its presence, but, as explained below, to the reactive nature of the components of the molecule of which it now forms a part. Inspection of the analytical results given below and in the earlier numbers of this series will show that: (1) Carbon and hydrogen estimations are not interfered with by the presence of thallium. (2) Thallous salts of organic acids analyse well: occasional high hydrogen values suggest the presence of water of crystallisation. (3) The hydrogen values for chelate thallous compounds are usually good, but irregular carbon figures suggest the presence of thallous salts resulting from hydrolysis. (4) The percentages found for all three elements in chelate compounds of dialkylthallium are usually very good. This is associated with considerable stability. Like platinum catalyst poisons after Maxted has rendered them harmless (*J.*, 1940, 252), all the electronic shells round all the constituent atoms have been completed, and they no longer attract or are attracted by other molecules as much as those in which this is not the case. This is *mutatis mutandis* the Cambridge conception of the survival of the unattractive (Thomson, *Phil. Mag.*, 1921, **41**, 530) and their stability clearly marks the end-points of the reactions leading to their formation. This is, however, not so well marked with the thallous derivatives of the sugars. The sugars are easily oxidised, and univalent thallium is not only easily reduced to the metal but is also easily oxidised to the tervalent state, and is thus an oxygen carrier. Any thallous derivative of the sugars is thus liable to change, and it may change, if care be not taken, under the conditions of preparation. This instability makes them difficult to analyse as accurately as might be wished, but it also makes them useful synthetic agents.

EXPERIMENTAL.

Thallous Derivatives of Hydroxy-acids.—On adding *N*-thallous or -potassium hydroxide to *N*-solutions of tartaric or mesotartaric acid, the precipitation of the acid salt followed by the formation of the normal salt, which dissolves, follows the same course with both alkalis up to the point of neutrality (phenolphthalein). Here the resemblance ends. The first drop of thallous hydroxide in excess leads to precipitation of tetrathallium tartrate (Part II) or of *tetrathallium mesotartrate*, heavy white compact crystals, sparingly soluble and slowly darkened by light [Found: Tl (by titration), 42.41. $C_4H_2O_6Tl_4$ requires Tl, 41.14%].

A few analyses of known thallous tartrates and salts of other carbon acids are here given to illustrate the accuracy to be expected:

	Found.			Calc.		
	C, %.	H, %.	Tl, %.	C, %.	H, %.	Tl, %.
Thallous hydrogen mesotartrate, $C_4H_2O_6Tl$	13.9	1.7	—	13.6	1.4	—
Thallous tartrate, $C_4H_4O_6Tl_2$	8.9	0.85	73.2	8.6	0.7	73.4
Tetrathallium tartrate, $C_4H_2O_6Tl_4$	5.06	0.4	42.65 * 84.6 †	5.0	0.2	42.4 * 84.9 †
Thallous carbonate, Tl_2CO_3 :						
(commercial sample)	2.76	0.24	87.3	2.51	0	87.2
(recrystallised)	2.78	0.19	—	—	—	—
Thallous formate, CHO_2Tl	4.9	0.8	82.15	4.8	0.4	81.95
Thallous fumarate } $C_4H_2O_4Tl_2$	9.3	0.56	77.9	9.2	0.4	78.2
Thallous maleate }	9.4	0.4	77.8			
Thallous succinate, $C_4H_4O_4Tl_2$	9.2	0.85	77.6	9.16	0.76	77.9

* By titration.

† As iodide.

Although these results conform to the usually accepted standards of accuracy, it will be seen that where the molecular weights of normal and tetrathallium tartrates, for instance, are 556.8 and 963.6 respectively, they are inadequate to indicate the presence or absence of small quantities of water of crystallisation, probably influencing, as mentioned above, the course of alkylations. It may be mentioned in this connection that thallium hydrogen *d*-tartrate is described in the literature as anhydrous, while the *mesotartrate* is said to crystallise as a hemihydrate. In alkaline solution the behaviour of the metal resembles that of lead and antimony. The resemblance between tetrathallium and a double tartrate of thallium and antimony has already been pointed out in Part II (p. 2369), and comparison may also be made with a basic lead tartrate $\text{Pb}_2\text{C}_4\text{H}_2\text{O}_6\cdot\text{H}_2\text{O}$ (Beilstein's "Handbuch", Vol. 3, p. 501).

Dithallium glycolate. Glycollic acid was neutralised by thallous hydroxide solution, and a further equal volume was then added. Compact colourless crystals of *dithallium glycolate* slowly separated, resembling, but more soluble than, tetrathallium tartrates, and like them, darkened by light [Found: Tl (by titration), 42.1. $\text{C}_2\text{H}_2\text{O}_3\text{Tl}_2$ requires Tl, 42.4%].

From a solution of glycollic acid accurately neutralised with thallous hydroxide (phenolphthalein) were obtained on evaporation needles of the very soluble normal salt described by Fahlberg (*J. pr. Chem.*, 1873, 7, 339). From a solution of lactic acid neutralised with thallous hydroxide a colourless syrup was obtained on evaporation, which did not crystallise; but on evaporating a solution to which twice the amount of hydroxide necessary for neutralisation had been added, as above, *dithallium lactate* slowly separated on nucleation with a sample obtained by rapid evaporation in a test-tube, in large, highly refracting, colourless crystals [Found: C, 7.6, 7.8; H, 0.91, 1.03; Tl (by titration), 39.4. $\text{C}_2\text{H}_2\text{O}_3\text{Tl}_2$ requires C, 7.25; H, 0.8; Tl, 41.15. $\text{C}_3\text{H}_4\text{O}_4\text{Tl}_2\cdot\text{H}_2\text{O}$ requires C, 7.0; H, 1.2; Tl, 39.7%].

The above basic salts are all colourless. Yellow hexathallium gluconate was described in Part III (p. 189). Saccharic acid also gives a substance approximating in composition to hexathallium saccharate, the way to which lies through *thallium hydrogen saccharate*, now described.

Crude brown potassium hydrogen saccharate (19 g.) was dissolved in water and partly neutralised with thallous hydroxide. The dark brown liquid was then boiled with animal charcoal, and considerable excess of thallous hydroxide added to the almost colourless filtrate. The solution was then made slightly acid with acetic acid, and again boiled with animal charcoal, filtered hot, and cooled. Crude thallium hydrogen saccharate (14.8 g.) separated, which probably contained a little potassium, as the titration value corresponded to 101.3% of thallium hydrogen saccharate. After recrystallisation from hot water, however, 2.126 g. required 5.11 c.c. of *N*-thallous hydroxide (calc., 5.14 c.c.), indicating 99.4% purity (Found: C, 18.3; H, 2.3. $\text{C}_6\text{H}_8\text{O}_7\text{Tl}$ requires C, 17.4; H, 2.2%). The neutral solution obtained by titration gave a glass on evaporation to dryness, thus resembling the normal lactate and also recalling Hirst and Purves's attempt to prepare normal thallium *xylotrimethoxyglutaric acid* (*J.*, 1923, 123, 1358). The syrup was then redissolved, and on the addition of four further equivalents of thallous hydroxide an amorphous yellow precipitate came down, more being obtained by adding alcohol to the filtrate. These on titration showed 52.24% and 50.74% of thallium, respectively. Hexathallium saccharate should contain 85.74% of thallium of which two-thirds or 57.16% should be titratable. It is possible that, on the lines indicated in Part III for the similar yellow hexathallium compounds of gluconic acid and of sorbitol, better analytical results could be obtained. But it is already evident that again the close resemblance between thallous and potassium salts in neutral or acid solutions persists. On making the solution alkaline with thallous hydroxide, more sparingly soluble substances are formed. From hydroxy-acids containing 2, 3, and 4 carbon atoms, these are colourless. From acids and alcohols containing 6 carbon atoms they are yellow. As will be seen below, this yellow colour already appears in the derivatives of ethylene glycol and of glycerol. (Solid TlOH is also yellow.)

Normal *thallous mucate* is easily prepared by neutralising the acid. It is sparingly soluble but can be crystallised from hot water. Its analysis is a good example of the general rule that the more sparingly soluble an organic thallium salt is the better does it analyse (Found: C, 11.8; H, 1.35. $\text{C}_6\text{H}_8\text{O}_7\text{Tl}_2$ requires C, 11.7; H, 1.3%).

Thallous Derivatives of Polyhydric Alcohols.—Sparingly soluble, of definite composition, yellow and darkened by light are *trithallium glycerol* and *tetrathallium erythritol*. A typical preparation is the following. Tetrathallium erythritol (51.1 g., 71.6%) crystallised after some hours' standing from a solution containing erythritol (9.3 g.), 6*N*-thallous formate (50 c.c.), 6*N*-sodium hydroxide (50 c.c.) and water (150 c.c.) (Found: C, 5.10; H, 0.76; Tl, 87.0. $\text{C}_4\text{H}_8\text{O}_4\text{Tl}_4$ requires C, 5.13; H, 0.65; Tl, 87.4%). The *glycerol* compound was prepared similarly (Found: C, 5.18; H, 0.70; Tl, 87.7. $\text{C}_3\text{H}_8\text{O}_3\text{Tl}_3$ requires C, 5.18; H, 0.72; Tl, 87.3%).

Thallium compounds of ethylene glycol. De Forcrand (*Compt. rend.*, 1923, 176, 20) described monothallium ethylene glycol prepared from thallous ethoxide and ethylene glycol as a beautiful precipitate closely resembling dehydrated uranium nitrate. He prepared the glycerol derivative, $\text{C}_3\text{H}_8(\text{OH})_2\text{OTl}$, similarly but did not report analyses. Chablay (*Ann. Chim.*, 1917, 8, 185) prepared dithallium ethylene glycol from monosodium ethylene glycol and thallous nitrate, both dissolved in liquid ammonia. According to him, monothallium ethylene glycol is first formed, 2 mols. of which interact with formation of ethylene glycol and the disubstituted compound. Chablay noted that the compound is soluble in water and that the metal can be determined by titration. He also described a dithallium mannitol made in the same way. Several preparations have now been made of a yellow substance crystallising from weighed quantities of ethylene glycol dissolved in equivalent amounts of aqueous thallous hydroxide. From 2*N*-solutions yellow crystals were obtained, the mother-liquor from which was 0.92*N* at room temperature. Analyses indicated that they were a mixture of approximately 2 mols. of dithallium ethylene glycol with 1 mol. of thallous hydroxide [Found: C, 4.14, 4.00, 3.80; H, 0.95, 0.94, 0.85; Tl, 87.7, 88.7. Calc. for $\text{C}_2\text{H}_4\text{O}_2\text{Tl}_2$: C, 5.12; H, 0.86; Tl, 87.2. Calc. for TlOH : C, 0; H, 0.45; Tl, 92.3. Calc. for $2(\text{C}_2\text{H}_4\text{O}_2\text{Tl}_2)\cdot\text{TlOH}$: C, 4.17; H, 0.79; Tl, 88.9. Calc. for $2(\text{C}_2\text{H}_4\text{O}_2\text{Tl}_2)\cdot\text{TlOH}\cdot\text{H}_2\text{O}$: C, 4.11; H, 0.95; Tl, 87.5%].

Similar results were obtained with pentaerythritol. This alcohol (6 g.) was dissolved in water (20 c.c.) and filtered hot, and thallous ethoxide (44.6 g.; 1 equiv. for each hydroxyl group) was also dissolved in water (60 c.c.), boiled, and filtered hot; on being mixed, the solution became yellow, and, on cooling,

crystals having the appearance of those of thallous hydroxide separated. The whole was then boiled down to half bulk. On cooling, a heavy, yellow, sandy powder separated which adhered firmly to the sides of the flask. This was separated with some difficulty and filtered through a weighed Gooch crucible, washed with alcohol and ether, and dried in a vacuum over phosphoric oxide for 24 hours (Substance A; 18.65 g.) [Found: C, 4.67; H, 0.9; Tl 86.96. Calc. for $C_6H_8O_4Tl_4$: C, 6.32; H, 0.85; Tl, 86.1. Calc. for $C_6H_8O_4Tl_4 \cdot TiOH \cdot H_2O$: C, 5.05; H, 0.93; Tl, 86.0%]. A further 8.5 g. were similarly obtained by adding alcohol to the filtrate (Substance B) [Found: C, 4.82; H, 0.93; Tl (titration), 86.09; Tl (iodide), 87.65%]. The substance obtained from ethylene glycol is thus slightly less soluble than thallous hydroxide, and that from pentaerythritol slightly more soluble. All three solubilities are of the same order, and both alcoholic derivatives appear to form mixed crystals with the hydroxide.

Dithallium trimethylene glycol (23 g.; 95.3%) was obtained as a light yellow precipitate on adding thallous ethoxide (25 g.) in ether to trimethylene glycol (3.8 g.). It was soluble in water but not in benzene (Found: C, 7.61; H, 1.50; Tl, 84.2. $C_3H_8O_3Tl_2$ requires C, 7.46; H, 1.25; Tl, 84.7%).

The thallous derivatives of the hexahydric alcohols resemble those of the di-, tri-, and tetra-hydric alcohols in being yellow and coloured more deeply by light. They differ from them in that they are precipitated instantly on mixing the respective solutions and in being amorphous.

From mixed 2N-solutions containing approximately 1 equiv. of thallous hydroxide for each hydroxyl group of inositol (m. p. 225°) a heavy yellow precipitate of *hexathallium inositol* was obtained [Found: Tl (titration), 87.36. $C_6H_8O_6Tl_6$ requires Tl, 87.6%. $C_6H_8O_6Tl_6$ requires Tl, 85.37%. $C_6H_8O_6Tl_6$ requires Tl, 82.11%]. On adding a slight excess of N-sodium hydroxide to the solution resulting from the above titration a similar yellow solid separated [Found: Tl (titration), 83.5%]. From N-solution the replacement of hydrogen by thallium is not so complete (Found, for precipitate from inositol and 1.1 equivs. of TiOH for each hydroxyl group: C, 5.62; H, 0.58; Tl, 85.75. $C_6H_8O_6Tl_6$ requires C, 5.614; H, 0.43; Tl, 87.6%. $C_6H_8O_6Tl_6$ requires C, 6.01; H, 0.58; Tl, 85.37%).

Inositol has no terminal groups which can be oxidised, and of 0.0298 equiv. of thallous hydroxide taken in this last experiment 0.0297 equiv. was accounted for by titration of the solid and of the mother-liquor. In a comparative experiment using glucose and working in the cold, 7.4% of the titratable thallium disappeared, having been neutralised by acid products of oxidation.

From mannitol and dulcitol and 1 equiv. of thallous hydroxide for each hydroxyl group in approximately 1.3N-solution, yellow derivatives were obtained containing 85.94 and 84.05% thallium respectively by titration ($C_6H_{12}O_6Tl_6$, $C_6H_{10}O_6Tl_6$, and $C_6H_{10}O_6Tl_6$ require respectively Tl, 87.45, 85.23, and 82.11%). The dulcitol compound is coloured brown by light: the inositol compound is turned black. Of the three, the mannitol compound is least changed in colour by light.

The above observations suggest that the thallous derivatives of secondary polyhydric alcohols tend to be less soluble than those of primary, that in the more sparingly soluble derivatives replacement of hydroxyl hydrogen by the metal occurs, but that in cases where the solubility is of the same order as that of the hydroxide addition of thallous hydroxide and of water also takes place. In addition to this, as pointed out on p. 1378, complete substitution of hydrogen by the metal does not always occur from aqueous solutions in more complicated molecules. The derivatives of sucrose, a disaccharide containing eight hydroxyl groups, of which three are primary, and of salicin, a phenolic glucoside containing five hydroxyl groups of which two are primary, are now discussed in the light of the above remarks.

(i) A typical preparation of the *thallous* derivative of sucrose is the following. Sucrose (8.8 g.) was dissolved in water (8 c.c.), cooled, and mixed with 1.275N-aqueous thallous hydroxide solution (68.5 c.c.), i.e., 5 equivs. per mol. of sucrose. After about 2 minutes the mixture became cloudy, and after an hour the white solid separating was filtered off at the pump and kept on a tile in a vacuum over sulphuric acid, taking 4 days to attain constant weight (22.5 g.) [Found: Tl (titration), 70.7; Tl (as iodide), 71.6. $C_{12}H_{22}O_{11}Tl_4$ requires Tl, 70.7%]. On drying, the solid turned yellow. A sample of thallous hydroxide placed in a dry tube at 100° turns black owing to formation of thallous oxide (Tl_2O), whilst the colour of the sucrose compound is unchanged by this treatment.

Preparations carried out with 4 equivs. of the hydroxide to one of sucrose gave substances of similar appearance but of slightly lower thallium content. For instance, 284.6 g. (yield 71.7%) [Found: Tl (titration), 69.9; Tl (as iodide), 68.7%] were obtained from 117.4 g. of sucrose and 4 equivs. of 1.26N-thallous hydroxide. Higher proportions of the hydroxide did not give rise to a corresponding increase of the thallium content, for on treating sucrose with 8 equivs. followed by slow evaporation in a vacuum the first crop separating contained 71.2% of thallium, determined as iodide. The carbon percentages, however, were low and those for hydrogen high. A nearer approach to the observed percentages is afforded by the formula $(C_{12}H_{20}O_{11}Tl_3)_2 \cdot 3TiOH \cdot H_2O$ or $(C_{12}H_{20}O_{11}Tl_3)_2 \cdot TiOH \cdot 3H_2O$, both adding up to $C_{24}H_{40}O_{22}Tl_6$, which requires C, 11.13; H, 1.67; Tl, 71.5% (Found, for two typical samples: C, 11.14, 11.57; H, 1.98, 1.78; Tl, 70.7, 71.6%) and both similar to the results found for the derivatives of ethylene glycol and pentaerythritol.

It is of interest to compare these results with those of Mackenzie and Quin (J., 1929, 951) and of Percival (J., 1935, 648).

(ii) Salicin (3 g.) and thallium hydroxide crystals (9 g.; 3.9 equivs.) were dissolved separately in water, and the solutions mixed and heated; on cooling and addition of alcohol, 7.5 g. of a light yellow substance separated (Found: C, 17.27; H, 1.99; Tl, 64.2%). On evaporation of the solution in a vacuum desiccator, white crystals separated which turned yellow on drying (Found: C, 17.27; H, 1.92; Tl, 63.6%). The mother-liquor yielded a white precipitate on addition of alcohol. These also turned yellow on drying (Found: C, 16.87; H, 1.94; Tl, 63.2. $C_{12}H_{18}O_7Tl_2$ requires C, 17.4; H, 1.65; Tl, 68.4%. $C_{12}H_{18}O_7Tl_2 \cdot 2H_2O$ requires C, 16.73; H, 2.05; Tl, 65.8%).

Surgical cotton-wool (1.71 g., dried over phosphoric oxide. Found: C, 42.7; H, 6.18. Calc. for cellulose: C, 44.44; H, 6.18%) was placed in 1.52N-thallous hydroxide solution and left for 24 hours. The product was then washed repeatedly with alcohol, which converts excess thallous hydroxide into the ethoxide which then dissolves in the alcohol. The product was unchanged in appearance but became yellow on drying, when it weighed 8.24 g. [Found: C, 9.58; H, 1.41; Tl (titration), 73.1;

Tl (as iodide), 75.3%]. In another experiment 4.35 g. of the same cotton-wool were boiled with 1.52N-thallous hydroxide for 15 minutes, washed with alcohol, and dried as before. The dried product weighed 17.36 g. [Found: C, 11.29; H, 1.67; Tl (titration), 63.5; Tl (as iodide), 72.4. Dithallium cellulose requires C, 12.66; H, 1.41; Tl, 71.88%. Trithallium cellulose requires C, 9.32; H, 0.91; Tl, 79.41%. $(C_6H_8O_5Tl_2)_2 \cdot 10H_2O$ requires C, 10.3; H, 1.52; Tl, 73.25%]. In view of the uncertain composition of the cotton-wool used, these results cannot be considered as more than indicating a possible point of departure with pure cellulose should this ever prove to be obtainable.

The basic thallous compounds described above are to be classified as salts, for they are, in the main, insoluble in non-hydrolytic solvents and soluble in water; they are also likely to char on heating without melting (cf. Sidgwick and Brewer, *J.*, 1925, 127, 2379). Thallous methoxide is intermediate. The thallous derivatives of the other normal primary alcohols have definite m. p.s and are more soluble in organic solvents than in water. The basic salts described, however, do resemble many chelate compounds in being stable to alkalis. This property is shared by acetals, and, as was described in Part X, several of the dialkylthallium derivatives of β -diketones are volatile in steam from alkaline solutions. This took place much more easily with the derivatives of dipropionylmethane than with those of acetylacetone. Further, beryllium dipropionylmethane (see below) is volatile in steam in the presence of a little ammonia while beryllium acetylacetone is not. It is not clear whether these facts are really connected.

Beryllium dipropionylmethane is readily made by heating beryllia with the diketone in benzene until the distillate is clear, filtering the residue from excess of beryllia, distilling off the benzene, and finally distilling the residue in a water-pump vacuum; m. p. 63° (Found: C, 62.5; H, 8.46. Found, after distillation in steam, and drying: C, 61.9; H, 8.4. $C_{14}H_{22}O_4Be$ requires C, 63.8; H, 8.4%). It closely resembles beryllium acetylacetone, but is inconveniently soluble in ether, and is better recrystallised from ligroin. On boiling with water containing a little ammonia it distills with the steam essentially unchanged. This does not happen with beryllium acetylacetone.

Action of Air, Light, and Moisture on Thallous Derivatives of Cotton-wool, Salicin, and Sucrose. (Adapted from a report by E. R. WILTSHIRE.)—The observation that the yellow colour of these compounds either appeared on or was intensified by drying led to an examination of the effect of exposing them to a moist atmosphere. Light caused darkening of the first compound. The experiments were therefore carried out by leaving the substances over water in closed vessels in the dark. In each case the yellow colour was gradually lost. As many of the dialkylthallium derivatives are lighter in colour than the corresponding derivatives of the non-alkylated metal, it is reasonable to suppose that this loss of colour is due to the attachment of water to the metal. The precipitate, for example, obtained by passing hydrogen sulphide through a solution of a thallous salt is black, but a white precipitate is obtained from dialkylthallous salts. No information, however, as to the existence of definite hydrates could be obtained from the increase of weight, as the absorption of water appeared to continue indefinitely. After one month the three derivatives gained 44, 58, and 18%, respectively.

A similar experiment was then carried out with a thallium derivative of more definite composition. Thallous fumarate gained the equivalent of 1 mol. of water after 50 days and of 2 mols. after three months. Diethylthallium fumarate gained 3% in 23 days, 1 mol. of water corresponding to 2.4%. In Part II it was shown that thallous 2-methylpyridine-3:4:6-tricarboxylate gained the equivalent of 1 mol. of water in 6 days, after which the weight became constant.

Exposure of thallium derivatives to a moist atmosphere. In each case, a weighed amount of the substance was placed on a watch-glass in a receptacle containing water in the dark:

A.	Thallium cellulose.	Thallium salicin.	Thallium sucrose.
Original wt., g.	0.823	0.517	1.967
Increase after 1 month, g.	0.366	0.302	0.358
" " 1 month, %	44.47	58.4	18.2

The colour in each case gradually disappeared, and finally darkening began to take place. None of the substances came to constant weight.

B.	Thallous fumarate.		Diethylthallium fumarate.	
	G.	%.	G.	%.
Original weight	6.617	—	0.599	—
Increase in wt. after 20 days	0.144	2.2	0.017	3.0
" " " 50 "	0.219	3.3	—	—
" " " 3 months	0.452	5.8	—	—
Calc. for addition of 1 mol. of H_2O	—	3.45	—	2.4

Constant weight was not obtained, but in each case exposure to the atmosphere quickly caused reversion to the original weight.

Dimethyl- (Found: C, 16.32; H, 2.46. Calc. for $C_8H_{14}O_4Tl_2$: C, 16.46; H, 2.42%) and diethylthallium fumarates (Found: C, 22.58; H, 3.37. Calc. for $C_{12}H_{22}O_4Tl_2$: C, 22.6; H, 3.48%) were prepared respectively in 52 and 56% yields by double decomposition between thallous fumarate and the dialkylthallium iodide in boiling water.

The Dialkylthallium Tartrates.—These can be prepared by neutralising tartaric acid with aqueous solutions of the dialkylthallium hydroxides. 4.196 G. of tartaric acid are theoretically required to neutralise 235 c.c. of 0.238N-diethylthallium hydroxide: the weight required lay between 4.1 and 4.19 g. The solution was filtered and evaporated to small bulk on the water-bath. The compound is very soluble in water. On concentration, four crops were obtained: (1) 3.1 g., (2) 6.95 g. on concentrating the aqueous solution. On adding methyl alcohol to the filtrate from crop (2), 3.7 g. were obtained

(crop 3), and finally 2.5 g. on evaporating to dryness (crop 4). Crops 2 and 3 were analysed (Found, respectively: C, 22.4, 19.2; H, 3.17, 3.35. Calc. for $C_{12}H_{24}O_6Tl_2$: C, 21.58; H, 3.63%).

Treatment of diethylthallium tartrate with methyl iodide. 2.63 G. of the tartrate were refluxed with methyl iodide for 17 hours; on removal of the methyl iodide, extraction with ether, filtration, and evaporation of the ether, 0.48 g. of syrup was obtained together with 2.9 g. of colourless diethylthallium iodide, corresponding to 58.3% of thallium in the diethylthallium tartrate taken (Calc.: Tl, 61.3%). As this was evidence that the methylation did proceed, the preparation was then repeated with 11.7 g. of the tartrate. A syrup was obtained which was distilled in a water-pump vacuum; the distillate solidified on nucleation with an authentic sample of dimethyl tartrate (Found: C, 40.85; H, 5.72. Calc.: C, 40.45; H, 5.52%).

Dipropylthallium tartrate. This can be prepared from normal thallous tartrate and dipropylthallium bromide by boiling them together with water. The substance (Found: C, 27.13; H, 4.42. $C_{18}H_{36}O_6Tl_2$ requires C, 26.34; H, 4.42%) is very soluble both in water and in benzene. Probably connected with this is the fact that on evaporating an aqueous solution on a water-bath, crystallisation first begins on the surface of the solution. This also takes place with solutions of diethylthallium tartrate. This surface crystallisation is also characteristic of the dialkylthallium halides, and in their case takes place in a very regular pattern (*Nature*, 1931, 907). The floating crystals are probably visible examples of McBain's ionic micelles.

Attempts to prepare tetrakis-dimethyl- and -diethyl-thallium tartrates by heating tetrathallium tartrate with the respective dialkylthallium halide resulted in the formation of the trisdialkylthallium tartrates only; the incomplete substitution which appears in the thallous compounds of more complicated substances now occurs in the simple tartaric acid molecule, the effective size of the metal having been increased and its strength as an alkali reduced by alkylation.

Treatment of tetrathallium tartrate with dimethylthallium bromide. 4.82 G. (1 equiv.) of the tartrate were boiled with 6.3 g. (4 equivs.) of the bromide. The solution was cooled, filtered from thallous bromide, and concentrated to small bulk. 0.16 G. of sparingly soluble substance, probably unreacted bromide, was filtered off, and then on adding alcohol 2.4 g. of a white precipitate of *trisdimethylthallium tartrate* were obtained [Found (titration): Tl, 22.8. $C_{10}H_{21}O_6Tl_3$ requires Tl (titration), 24.0%]. Another portion, washed with alcohol and acetone and dried in a vacuum, contained Tl, 23.4% (by titration).

Treatment of tetrathallium tartrate with diethylthallium iodide. 12 G. of the tartrate were heated in water with excess of the iodide. Two crops were obtained, containing severally Tl, 20.75, 23.16% (by titration). On addition of potassium iodide to a solution, diethylthallium iodide was recovered corresponding to 66.64% of thallium [*trisdiethylthallium tartrate*, $C_{16}H_{38}O_6Tl_3$, requires Tl (total), 65.63; Tl (by titration), 21.88%].

Part of this work has been carried out by the writer during the last year in Professor Kendall's Department in Edinburgh, whose kindness and hospitality as also that of Dr. Neil Campbell, of Dr. E. G. V. Percival and of everyone else in the department, he wishes gratefully to acknowledge. Part of it also is taken from unpublished notes left in his hands by Miss C. M. Fear and Mr. E. R. Wiltshire.

The writer wishes to thank Professor E. L. Hirst and Dr. E. G. V. Percival for useful criticism.

Acknowledgment is also made to the Colston Society of the University of Bristol for their continuous generosity during a term of fourteen years.

The author also wishes to thank Mr. Gilbert Allen, of Bristol University, who safeguarded his materials and preparations all through the War.

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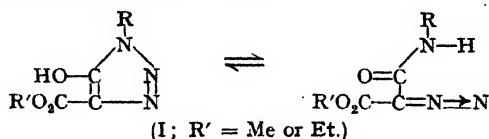
[Received, November 29th, 1946.]

257. *The Mechanism of the Tautomeric Change of 5-Hydroxy-1:2:3-triazole-4-carboxylic Esters into Aliphatic Diazo-compounds.*

By B. R. BROWN and D. LL. HAMMICK.

Dimroth (*Annalen*, 1904, **335**, 1; 1905, **338**, 143; 1910, **373**, 336) interpreted the kinetics of this reaction as showing that the change takes place in the un-ionised enol molecule. A reconsideration of his data indicates that the change is bimolecular, involving a proton and an enol ion. The electronic processes involved in the proposed mechanism are deduced from a comparison of rate constants for various substituted triazole esters.

THE reaction under consideration is the following:



which was established by Dimroth (*loc. cit.*). Owing to the fact that the enolic triazole tautomer is acidic, he was able to study the kinetics of the forward reaction and the equilibrium in various solvents. He interpreted his results as showing that the reaction is unimolecular

with respect to the enol, and concluded that the change from enol to neutral form takes place in the un-ionised enol molecule. His evidence (*Annalen*, 1904, **335**, 60) was the observed proportionality between the rate in the presence of various concentrations of the sodium salt of the enol, and the amount of undissociated enol as calculated from the "degree of dissociation" of the sodium salt obtained from conductivity data. His conclusion is invalid on account both of this fallacious "degree of dissociation", and of the occurrence of an appreciable salt effect.

A reconsideration of Dimroth's results in the light of more recent ionic and kinetic theory shows that the reaction is in reality a bimolecular process involving a hydrogen ion and an enol ion. Thus his values (*ibid.*, p. 53) for the rate constants in the presence of water and of 0.06N-sodium chloride :

$$\begin{aligned} k \text{ (mins.}^{-1}\text{) at } 50^\circ \text{ in water (I; R = phenyl)} &= 0.00128 \\ k \text{ (mins.}^{-1}\text{) at } 50^\circ \text{ in 0.06N-NaCl (I; R = phenyl)} &= 0.00106 \end{aligned}$$

reveal a negative salt effect and indicate that the reaction is between two oppositely charged ions. Also his unimolecular rate constants increase as the concentration of either the hydrogen ion or the enol ion increases (*ibid.*, p. 54) :

$$\begin{aligned} k \text{ (mins.}^{-1}\text{) at } 50^\circ \text{ in water (I; R = phenyl)} &= 0.00128 \\ k \text{ (mins.}^{-1}\text{) at } 50^\circ \text{ in dilute HCl (I; R = phenyl)} &= 0.00195 \end{aligned}$$

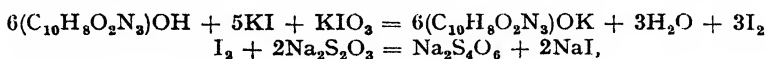
Mols. of Na salt of enol : mols. of enol.	k (mins. ⁻¹).
0 : 1	0.00128
1 : 1	0.00195
2 : 1	0.00225
4 : 1	0.00267
8 : 1	0.00306

Addition of alkali causes an increased rate of reaction by increasing the concentration of enol ion. This fact is remarked upon by Dimroth (*ibid.*, p. 3), and prevents an ordinary alkali titration being used to follow the reaction.

Following up this evidence, Dimroth's results (*ibid.*, p. 49) for the tautomerism of (I; R = phenyl) in water have been recalculated using a bimolecular rate equation. His values (*ibid.*, 1905, **338**, 175; 1904, **335**, 57) for the dissociation constant of this compound in water are :

$$\begin{aligned} K \text{ at } 25^\circ &= 1.6 \times 10^{-2} \\ K \text{ at } 50^\circ &= 1.3 \times 10^{-2} \end{aligned}$$

whence the value at 40° is estimated at 1.4×10^{-2} . Using these dissociation constants and the following equations for the estimation of the enol,



the following typical sets of results were calculated :

25 C.c. of reaction mixture titrated against N/50-thiosulphate (temp., 50°).

Time (mins.).	Titre (c.c.).	$[\text{H}^+] = [\text{enol ion}]$ (mols./l.).	Bimol. k (mols./l./sec.).	Dimroth's unimol. constant $0.4343k$ (mins. ⁻¹).
0	18.55	0.884×10^{-2}		
60	17.10	0.834 "	1.88×10^{-3}	5.89×10^{-4}
120	15.85	0.789 "	1.94 "	5.69 "
180	14.68	0.747 "	1.92 "	5.65 "
300	12.62	0.667 "	2.05 "	5.57 "
400	11.13	0.607 "	2.15 "	5.54 "
		Average : 1.99 "		
		Average for a similar set at 50° : 1.88 "		

100 C.c. of reaction mixture titrated against N/10-thiosulphate (temp., 40.2°).

0	12.77	0.809×10^{-2}		
170	12.13	0.779 "	4.67×10^{-4}	1.31×10^{-4}
300	11.70	0.759 "	4.53 "	1.27 "
380	11.47	0.748 "	4.46 "	1.23 "
470	11.15	0.732 "	4.61 "	1.21 "
		Average : 4.57 "		

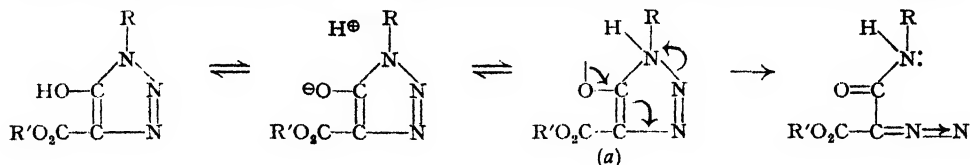
Whence, $k_{50^\circ} = 1.94 \times 10^{-3}$ and $k_{40.2^\circ} = 4.57 \times 10^{-4}$, both in mols./l./sec. Substitution in the equation $k = PZ e^{-E/RT}$ gives the following E and PZ values :

$$E = 29,660 \text{ cal.}$$

$$PZ = 10^{+17.3}$$

It is seen that the PZ value is one normally observed for a reaction between oppositely charged ions, viz., 10^{+13} to 10^{+19} (Bell, *J.*, 1943, 629), and therefore supports a bimolecular ionic mechanism.

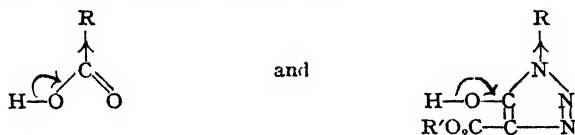
These considerations lead us to suggest the following picture of the tautomeric change :



Evidence that the electronic processes implied in (a) for the decomposition of the transition state are rate-determining is obtained by a consideration of the effects of substituents on the rate constants and on the equilibrium constants. These will be expected to parallel the dissociation constants of the enol, which in turn should parallel the dissociation constants of the corresponding acids, $R \cdot CO_2H$. That the latter is the case is evident from Dimroth's determination of the dissociation constants of various enol forms :

R.	$R \cdot CO_2H$. (Watson, "Modern Theories of Organic Chemistry," 2nd Edition, 1941, p. 27.)	Enol. (Dimroth, <i>Annalen</i> , 1905, 338, 175.)
Methyl	1.82×10^{-5}	0.3×10^{-2}
<i>p</i> -Tolyl	4.24 "	1.0 "
Phenyl	6.27 "	1.6 "
<i>p</i> -Bromophenyl	10.7 "	2.0 "

It is seen that the dissociation constants increase with the power of the group R to accept electrons, as expected for the comparable processes :



The electronic processes (a) in the proposed mechanism should likewise be facilitated by acceptor groups at R , and hence the rate and equilibrium constants (diazo-compound/triazole) should increase in the same order as the ionisation constants, i.e., with the accepting power of R . That this does occur is good evidence for the proposed electron shifts.

Values of K and k in ethyl alcohol at 25° .

(Dimroth, *Annalen*, 1910, 373, 349.)

R.	K .	k (mins. ⁻¹).
Benzyl	118	0.003×10^{-2}
<i>p</i> -Tolyl	120	0.94 "
Phenyl	300	1.02 "
<i>p</i> -Bromophenyl	555	4.58 "
<i>p</i> -Nitrophenyl	very large	60.0 "
2 : 4-Dinitrophenyl	not measurable	100.0 "

Thus Dimroth's kinetic data indicate that the reaction has an ionic mechanism, involving the attack of a proton on an enol ion, and furthermore, enable the nature of the electronic shifts involved to be elucidated with a fair degree of certainty.

We wish to thank Mr. R. P. Bell, F.R.S., for helpful criticism.

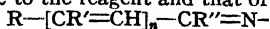
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[Received, December 3rd, 1946.]

258. The Absorption Spectra of 2:4-Dinitrophenylsemicarbazones.

By A. E. GILLAM and D. G. MOSS.

The absorption spectra of new and previously-prepared 2:4-dinitrophenylsemicarbazones of various aldehydes and ketones are recorded and shown to be, approximately, summation curves of the light absorption due to the reagent and that of the chromophore



where $n = 0, 1, 2$, or 3 and R, R' , and R'' may be either H or alkyl. The maxima of the subtraction curves suffer a steady displacement to longer wave-lengths as the conjugated system is lengthened.

IN earlier papers (*J.*, 1940, 1453; 1941, 815; 1943, 565; 1945, 432) light-absorption data on carbon compounds containing specific chromophoric groups such as those of unsaturated ketones and their semicarbazones and similar derivatives were collected and classified with the object, among others, of using the data in the determination of molecular structure. In the present communication the absorption spectra of 2:4-dinitrophenylsemicarbazones of various carbonyl compounds are recorded and an attempt is made to correlate the location of the absorption bands with the structure of the compounds and especially the length of the conjugated system present.

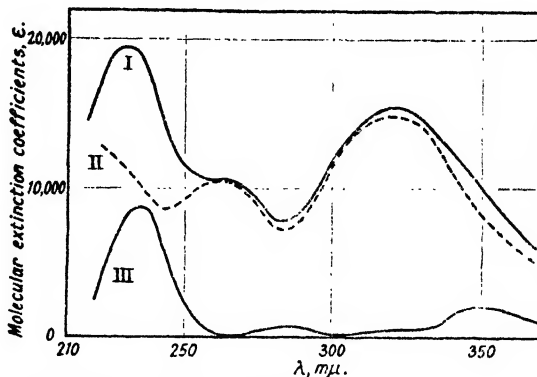
2:4-Dinitrophenylsemicarbazide was first prepared by Kniphorst (*Rec. Trav. chim.*, 1925, **44**, 724) who also showed that it formed condensation products with carbonyl compounds. McVeigh and Rose (*J.*, 1945, 713) have more recently shown that it can be used as a means of detection and characterisation of aldehydes and ketones generally, and have recorded the melting points of a number of derivatives of such compounds.

The molecules of these carbonyl derivatives contain two main chromophoric units, namely 2:4-dinitrophenylsemicarbazide itself and the substituted $>C=N-$ group formed by condensation of the carbonyl group with the active $-NH_2$ group of the semicarbazide. With $\alpha\beta$ -unsaturated ketone derivatives the chromophoric groups are those of the substituted semicarbazide itself and the $CR_2:CH:CR'_2N-$ group which is, in effect, the $-C=C-C=N-$ chromophore normally met with in simple semicarbazones (cf. Evans and Gillam, *J.*, 1943, 565). The work of Ramart-Lucas and her various collaborators (*Bull. Soc. chim.*, 1932, **51**, 289) has shown that in a compound having two unconjugated chromophores the light absorption approximates more nearly to a simple summation the more widely separated are the chromophores in the molecule. Thus in the 2:4-dinitrophenylsemicarbazones of unsaturated carbonyl compounds the two compound chromophores are unconjugated but not widely separated so that complete independence is not to be expected.

If we compare the absorption curves of the substituted semicarbazones of simple ketones with those of the corresponding derivatives of $\alpha\beta$ -unsaturated ketones and of dienones we would further expect to find that the summation curves contain a fixed component (the semicarbazide chromophore) and one which varies in the location of its band with the length of the conjugated system responsible for it. Thus in any observed absorption curve of a 2:4-dinitrophenylsemicarbazone if we subtract the known absorption of the reagent the resulting subtraction curve should be that of the $R-[CR'=CH]_n-CH=N-$ chromophore (where $n = 0, 1, 2, 3$, etc., and R and R' may be either H or alkyl groups).

The numerical data are given in Table I, whilst Figs. 1, 2, and 3 show the absorption curves of only a few of the more typical examples. The occurrence of low-intensity absorption bands between 270 and 360 $m\mu$ in some of the subtraction curves is still unexplained, but this does not appear to affect the main conclusions.

FIG. 1.



Absorption spectra in alcohol:

- I. cycloHexanone 2:4-dinitrophenylsemicarbazone.
- II. 2:4-Dinitrophenylsemicarbazide.
- III. Subtraction curve.

TABLE I.

Spectroscopic Data on 2 : 4-Dinitrophenylsemicarbazones.

Parent carbonyl compound.	$\lambda_{\max.}, \text{A.}$	$\epsilon.$	Subtraction curve.		No. of ethylene links or equivalent.	
<i>Simple aldehydes and ketones.</i>						
Acetaldehyde	{ 2285 2640 3200	19,400 12,600 16,500	2325	8,400	1	
Methyl ethyl ketone	{ 2275 2630 3200	20,000 11,800 15,900	2300	8,800		
Methyl <i>n</i> -propyl ketone	{ 2280 2650 3205	19,200 11,000 15,800	2300	8,000		
<i>cyclo</i> Hexanone	{ 2295 2640 3205	19,300 10,800 15,400	2325	8,400		
<i>$\alpha\beta$-Unsaturated aldehydes and ketones.</i>						
Mesityl oxide	{ 2600 3220	22,600 17,400	2600	12,000		2
3-Methylpent-3-en-2-one	{ 2600 3225	24,000 15,800	2610	13,600		
1-Methylcyclohexen-3-one	{ 2635 3235	29,800 19,400	2640	19,400		
Crotonaldehyde	{ 2625 3220	32,200 19,100	2640	21,800		
<i>Dienones.</i>						
ψ -Ionone	3075	40,000	3000	27,500	3	
Hepta-3 : 5-dien-2-one	2875	37,700	2850	30,100		
<i>Aromatic compounds.</i>						
Benzaldehyde	{ 2725 3145	23,800 22,300	2790	15,600	2½	
Acetophenone	{ 2650 3175	25,000 20,000	2650	14,800		
Cinnamaldehyde	3220	45,000	3250	30,200	3½	
Benzylideneacetone	3150	39,700	3100	25,300		
Citrylideneacetaldehyde	3290	41,500	3360	28,200	4	
2 : 4-Dinitrophenylsemicarbazide ...	{ 2610 3220	10,500 14,900	} —	—		

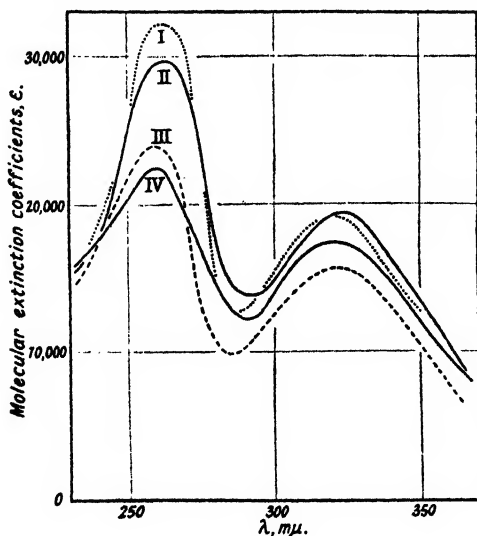


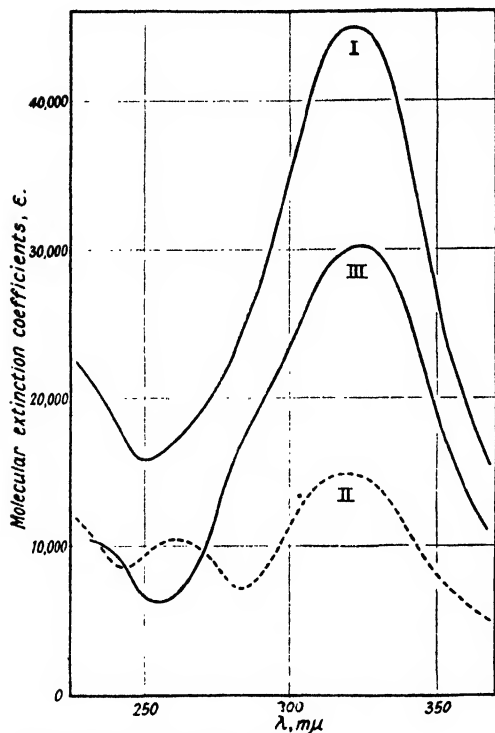
FIG. 2.

Dinitrophenylsemicarbazones (absorption spectra in alcohol):

- I. Crotonaldehyde.
- II. 1-Methylcyclohexen-3-one.
- III. 3-Methylpent-3-en-2-one.
- IV. Mesityl oxide.

The subtraction-curve data in Table I show the steady displacement of the maxima to longer wave-lengths as the length of the conjugated system in the non-semicarbazide part of the molecule increases. This is shown more clearly in Fig. 4. The fact that the two types of aromatic carbonyl derivative show displacements which are respectively equivalent to $2\frac{1}{2}$ and $3\frac{1}{2}$ ethylene linkages supports the suggestion of Kuhn, Hütsser, *et al.* (*Z. physikal. Chem.*, 1935, 29, B, 363) that a benzene nucleus in conjugation with one or more ethylene linkages is equivalent to $1\frac{1}{2}$ of such bonds.

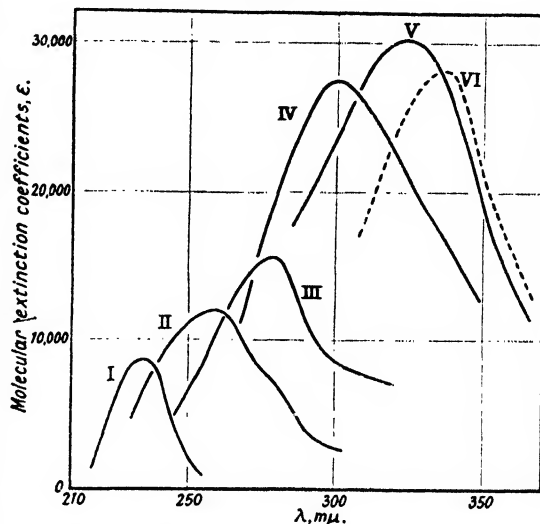
FIG. 3.



Absorption spectra in alcohol :

- I. Cinnamaldehyde 2 : 4-dinitrophenylsemicarbazone.
- II. Reagent.
- III. Subtraction curve.

FIG. 4.



2 : 4-Dinitrophenylsemicarbazone subtraction curves :

- I. Simple ketone (cyclohexanone).
- II. $\alpha\beta$ -Unsaturated ketone (mesityl oxide).
- III. Simple aromatic aldehyde (benzaldehyde).
- IV. Dienone (ψ -ionone).
- V. Unsaturated aromatic aldehyde (cinnamaldehyde).
- VI. Trienal (citrylidenecrotonaldehyde).

The validity of the generalisation that two unconjugated chromophores in a molecule produce an approximate summation of the effects due to each can be checked within this particular series, since the observed absorption of the 2 : 4-dinitrophenylsemicarbazones when

TABLE II.

Comparison of Direct Absorption Data on Semicarbazones with Subtraction Curves via the 2 : 4-Dinitrophenylsemicarbazones.

Parent carbonyl compound.	Direct absorption spectrum of semicarbazone.		Subtraction curve via 2 : 4-dinitrophenylsemicarbazone.	
	$\lambda_{\text{max.}}$, A.	ϵ .	$\lambda_{\text{max.}}$, A.	ϵ .
cycloHexanone	2295	11,200	2325	8,400
Mesityl oxide	2600	12,000	2600	12,000
Crotonaldehyde	2645	24,000	2640	21,800
1-Methylcyclohexen-3-one. ...	2655	25,700	2640	19,400
ψ -Ionone	2995	45,400	3000	27,500
Hepta-3 : 5-dien-2-one	2900	37,000	2850	30,100
Benzaldehyde	2825	19,900	2790	15,600
Acetophenone	2715	17,780	2650	14,800

corrected for the separate absorption of the reagent itself should yield a subtraction curve comparable with the known and directly observed absorption spectra of the simple semicarbazones. The available data are given in Table II, and, considering the number of variables concerned in obtaining the data, the general agreement is good, being better in terms of location of the band than where intensities are concerned. The values for ψ -ionone are noticeably discrepant in this latter respect.

EXPERIMENTAL.

1-Methylcyclohexen-3-one was prepared by condensation of formaldehyde and acetoacetic ester followed by ring-closure of the methylenediacetoacetic ester (Knoevenagel, *Annalen*, 1894, **281**, 94); b. p. 200°.

3-Methylpent-3-en-2-one was prepared by condensation of acetaldehyde and methyl ethyl ketone (Hinkel, *J.*, 1931, 817). The ketone was crystallised from benzene to constant m. p., but the N content was low (Found: N, 19.6. Calc.: N, 21.8%). This might have been due to retention of solvent as the spectroscopic data were quite normal. Attempted purification by chromatography gave slight evidence of lack of homogeneity, but no increase in purity was in fact achieved.

ψ -Ionone was prepared by condensation of acetone and citral (Stiehl, *J. pr. Chem.*, 1898, **58**, 79) and crystallised successively from chloroform and chlorobenzene.

We are indebted to Dr. E. R. H. Jones for a sample of citrylidene crotonaldehyde which was isolated from the products of the condensation of citral with crotonaldehyde (cf. Batty *et al.*, *J.*, 1937, 756; 1939, 1559). The specimen used had λ_{\max} , 3140 Å.; $\epsilon = 14,500$.

2:4-Dinitrophenylsemicarbazones.—These were prepared by dissolving 2:4-dinitrophenylsemicarbazide (0.5 g.) in alcohol (80 ml.) and adding to the boiling solution slightly less than the theoretical amount of the carbonyl compound dissolved in the minimum of alcohol. After addition of concentrated hydrochloric acid (2 drops) the solution was boiled for ten minutes after which the precipitated derivative was filtered off, being usually only very sparingly soluble in alcohol even at the boiling point. For recrystallisation chloroform was found to be the most useful solvent and derivatives were recrystallised to constant melting point, two or three crystallisations being usually sufficient. All the 2:4-dinitrophenylsemicarbazones in Table III are new except that of methyl ethyl ketone (cf. McVeigh and Rose, *loc. cit.*).

TABLE III.

2:4-Dinitrophenylsemicarbazones.

Aldehyde or ketone.	M. p. of deriv.	Formula.	Nitrogen, %.		Recrystallised from:
			Calc. or required.	Found.	
Methyl ethyl ketone	235° (decomp.)	C ₁₁ H ₁₃ O ₅ N ₅	23.7	23.7	Chloroform
Mesityl oxide	207	C ₁₃ H ₁₅ O ₅ N ₅	21.8	21.4	Chloroform
3-Methylpent-3-en-2-one ...	236.5	C ₁₃ H ₁₅ O ₅ N ₅	21.8	19.6	Benzene
1-Methylcyclohexen-3-one	227.5	C ₁₄ H ₁₆ O ₅ N ₅	21.0	20.7	Chloroform
ψ -Ionone	227	C ₂₀ H ₂₆ O ₅ N ₅	16.9	16.1	Chlorobenzene
Hepta-3:5-dien-2-one	240	C ₁₄ H ₁₄ O ₅ N ₅	21.0	20.4	Alcohol
Citrylidene crotonaldehyde	207 (no decomp.)	C ₂₁ H ₂₅ O ₅ N ₅	16.4	16.1	Alcohol

Absorption spectra were determined by standard methods using a Hilger E3 quartz spectrograph and a Spekker photometer. Purified alcohol was used as solvent throughout, although the very low solubility of the 2:4-dinitrophenylsemicarbazones made this difficult at times. The high intensity of absorption in some cases made it possible to use very dilute solutions for the determination, and the concentrations usually ranged between 0.03 and 0.003% only. The solutions were made by dissolving 2—3 mg. of the compound in hot alcohol, cooling, and making up to suitable volume, e.g., 100 ml. All determinations were made in duplicate, the λ_{\max} and ϵ_{\max} values being taken from the mean curves.

Our thanks are due to Miss McVeigh and Dr. F. L. Rose for specimens of a number of the compounds examined.

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[Received, December 19th, 1946.]

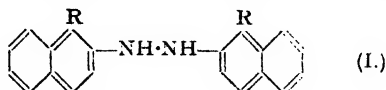
259. The Naphthidine Transformation involving β -Positions only.

By HERBERT H. HODGSON, JOHN HABESHAU, and P. B. R. MURTI.

1:1'-Dichloro- and 1:1'-dibromo-2:2'-diamino-3:3'-dinaphthyl are most probably formed in the reduction of 1:1'-dichloro- and 1:1'-dibromo-2:2'-azonaphthalene by stannous chloride in ethyl alcohol-hydrochloric acid solution. 1-Bromo-2-naphthalenediazoacetate decomposes at ordinary temperatures to give 1-bromo-2-naphthaleneazo- β -naphthol.

THE naphthidine transformations already reported have involved α - and $\alpha\beta$ -positions only (Nietzki and Goll, *Ber.*, 1885, **18**, 3254; Vesely, *Ber.*, 1905, **38**, 136; Meisenheimer and Witte, *Ber.*, 1903, **36**, 4153; Hodgson and Habeshaw, this vol., p. 77). It is of interest also that,

in the transformation of 1 : 1'-hydrazonaphthalene, the 2- and 4-positions exhibit approximately equal activity (cf. Hodgson and Habeshaw, *loc. cit.*) while no mixed 1 : 1'-diamino-2 : 4'-dinaphthyl has ever been detected among the transformation products. No change involving the 2 : 3- (*i.e.*, solely β -positions) transformation has hitherto been reported, and, in view of the fact that among the possible resonance structures of a 1 : 1'-substituted -2 : 2'-hydrazonaphthalene there is one (I) which indicates that such a change might be possible, it appeared of interest



to investigate whether this 2 : 3-naphthidine change would occur in the cases of 1 : 1'-dichloro- and 1 : 1'-dibromo-2 : 2'-hydrazonaphthalenes (I; R = Cl or Br) since such compounds might be formed intermediately by the action of stannous chloride in ethyl alcohol-hydrochloric acid suspensions of 1 : 1'-dichloro- and 1 : 1'-dibromo-2 : 2'-azonaphthalenes (cf. Cohen and Oesper, *Ind. Eng. Chem. Anal.*, 1936, 8, 306).

As anticipated, dinaphthyl formation occurred and in all probability 1 : 1'-dichloro- and 1 : 1'-dibromo-2 : 2'-diamino-3 : 3'-dinaphthyls were formed, so that the naphthidine transformation had taken place between β -positions only. When the reduction of the above halogeno-azo-compounds was carried out with stannous chloride and hydrochloric acid in the absence of ethyl alcohol, cleavage occurred between the nitrogen atoms of the azo-group, and 1-chloro- and 1-bromo-2-naphthylamine were formed respectively. The constitutions of the above dinaphthyls were tentatively established by the fact of dihydrochloride formation in the cases of the chloro- and bromo-compounds, and of the tetrazotisation of the 1 : 1'-dibromo-2 : 2'-diamino-3 : 3'-dinaphthyl and subsequent coupling with alkaline β -naphthol to give a bisazo-compound. Since halogens were not displaced, it is most unlikely that dinaphthyl formation would involve the 4 : 4'-positions.

When a solution of 1-bromo-2-naphthalenediazoacetate was allowed to decompose at ordinary temperatures, 1-bromo-2-naphthaleneazo- β -naphthol was produced, an indication that 1-bromo-2-naphthol must first have been formed, by hydrolysis of the diazoacetate, and that unchanged diazo-compound subsequently coupled with it in the 1-position by displacement of the 1-bromine atom.

EXPERIMENTAL.

1 : 1'-Dichloro-2 : 2'-diamino-3 : 3'-dinaphthyl.—1 : 1'-Dichloro-2 : 2'-azonaphthalene (5 g.) (compare Hodgson, Leigh, and Turner, *J.*, 1942, 744) was boiled gently with ethyl alcohol (50 c.c.) and a solution of crystallised stannous chloride (10 g.) in hydrochloric acid (25 c.c., *d* 1.18) added gradually with shaking. During this addition, all the solid passed into solution, and, after the mixture had been kept on the boiling water-bath for 10 minutes, it was cooled and then treated with hydrochloric acid (25 c.c., *d* 1.18); 1 : 1'-dichloro-2 : 2'-diamino-3 : 3'-dinaphthyl dihydrochloride then separated (1.6 g.) in colourless crystals which were filtered off and washed with ether; it was soluble in water, evolved hydrogen chloride on treatment with concentrated sulphuric acid with formation of a yellow solution, and decomposed on heating at *ca.* 400° (Found : Cl, 33.2. $C_{20}H_{16}N_2Cl_4$ requires Cl, 33.3%).

1 : 1'-Dichloro-2 : 2'-diamino-3 : 3'-dinaphthyl was obtained as a white flocculent precipitate, which coagulated somewhat on standing and became biscuit coloured, when warm aqueous sodium carbonate was stirred into a warm aqueous solution of the above dihydrochloride; it was filtered off, washed, dried, and crystallised from benzene-light petroleum (1 : 1) in small colourless needles, m. p. 121–122° (Found : N, 8.1; Cl, 19.8. $C_{20}H_{14}N_2Cl_2$ requires N, 7.9; Cl, 20.1%), which soon became discoloured in air and was moderately soluble in ethyl alcohol; the alcoholic solution, however, rapidly oxidised and became reddish-violet, a red film forming on the wall of the glass container.

Preparation of 1-Bromo-2-naphthylamine.—A solution of β -naphthylamine (28 g.) in glacial acetic acid (200 c.c.) containing acetic anhydride (25 c.c.) was heated on the boiling water-bath for 20 minutes to complete the acetylation, and then treated dropwise with the theoretical amount of bromine (32 g.) during continuous stirring. The resulting 1-bromoaceto-2-naphthalide was precipitated by dilution with water in quantitative yield, the precipitate dissolved in alcohol (250 c.c.), hydrochloric acid (30 c.c., *d* 1.18) added, and the mixture boiled for 6 hours to complete the hydrolysis; 1-bromo-2-naphthylamine was then precipitated by addition of 20% aqueous sodium hydroxide, purified by crystallisation from light petroleum, and obtained in colourless needles, m. p. 63° (Cosiner, *Ber.*, 1881, 14, 59, gives m. p. 63°) (Found : Br, 35.8. Calc. for $C_{10}H_7NBr$: Br, 36.0%).

1-Bromo-2-naphthaleneazo- β -naphthol, obtained by diazotisation of the above amine and coupling with alkaline β -naphthol in the usual way, crystallised from toluene in dark red parallelepipeds, m. p. 169–170° (Found : N, 7.5; Br, 21.0. $C_{20}H_{13}ON_2Br$ requires N, 7.4; Br, 21.2%), which gave with concentrated sulphuric acid a bright red-violet colour turning to crimson on dilution with water.

1-Bromo-2-naphthaleneazo- β -naphthylamine, obtained by diazotisation of the above amine in aqueous hydrochloric acid and coupling with an alcoholic solution of β -naphthylamine in the presence of acetic acid and sodium acetate (cf. Hodgson and Foster, *J.*, 1941, 755), crystallised from toluene in scarlet plates, m. p. 174–175° (Found : N, 11.3; Br, 20.8. $C_{20}H_{14}N_2Br$ requires N, 11.2; Br, 21.0%), which

gave with concentrated sulphuric acid a blue colour turning to red and then to orange-yellow on addition of water.

1:1'-Dibromo-2:2'-azonaphthalene.—A mixture of finely divided 1-bromo-2-naphthylamine (5 g.) in hydrochloric acid (25 c.c., *d* 1.18) and water (50 c.c.) was diazotised by addition of a solution of sodium nitrite (2 g.) in water (10 c.c.) with stirring at 0°, the resulting yellow solution filtered, treated rapidly under vigorous stirring with crystallised sodium acetate (40 g.) dissolved in the minimum amount of water to remove mineral acid, and then immediately followed by a solution of crystallised sodium sulphite (10 g.) in water (50 c.c.). A light brown precipitate immediately separated (5.7 g.), and after the mixture had been stirred for 30 minutes at room temperature, when no further reaction of the precipitate with alkaline β -naphthol was detected (absence of diazo-sulphite, cf. Hodgson and Marsden, *J.*, 1943, 470), it was heated to 60° and filtered. The precipitate of 1:1'-dibromo-2:2'-azonaphthalene crystallised from benzene in yellow plates, m. p. 193–195° (Found: N, 6.6; Br, 36.2. $C_{10}H_6Br_2N_2$ requires N, 6.4; Br, 36.4%), which gave with concentrated sulphuric acid a Bordeaux-red solution turning to scarlet on addition of water.

When the solution of 1-bromonaphthalenediazonium chloride above was treated with sodium acetate only, 1-bromo-2-naphthaleneazo- β -naphthol separated on keeping; it crystallised from toluene in red parallelepipeds, m. p. and mixed m. p. with authentic specimen 168–170° (Found: N, 7.5; Br, 21.0%). If an inadequate amount of sodium acetate is added before the sodium sulphite, the resulting 1:1'-dibromo-2:2'-azonaphthalene is mixed with the azo- β -naphthol dye above.

1:1'-Dibromo-2:2'-diamino-3:3'-dinaphthyl.—A suspension of 1:1'-dibromo-2:2'-azonaphthalene (5 g.) in ethyl alcohol (50 c.c.) was heated on the boiling water-bath during the gradual addition with vigorous shaking of a solution of crystallised stannous chloride (10 g.) in hydrochloric acid (25 c.c., *d* 1.18), and the boiling continued (30 minutes) until most of the suspended matter had passed into a nearly colourless solution. The mixture was filtered hot, cooled, hydrochloric acid (20 c.c., *d* 1.18) added, the precipitate (*a*) filtered off, and the solution kept; crystals (*b*) of 1:1'-dibromo-2:2'-diamino-3:3'-dinaphthyl dihydrochloride then separated. Crystals (*b*) were filtered off and washed with ether (Found: Ionic Cl, 13.6. $C_{20}H_{14}N_2Br_2 \cdot 2HCl$ requires Cl, 13.8%). Precipitate (*a*) and crystals (*b*) were repeatedly stirred with hydrochloric acid (5 c.c., *d* 1.18) and water (10 c.c.), aqueous sodium nitrite was added until a positive reaction for free nitrous acid was obtained, the mixtures were filtered, and the resulting solutions of 1:1'-dibromo-3:3'-dinaphthyl-2:2'-tetrazonium chlorides were stirred into alkaline β -naphthol; in each case 1:1'-dibromo-3:3'-dinaphthyl-2:2'-bisazo- β -naphthol separated; this compound crystallised from toluene in red micro-plates, m. p. 315° (Found: N, 7.6; Br, 21.1. $C_{40}H_{24}O_2N_4Br_2$ requires N, 7.4; Br, 21.3%), which give a brilliant blue-violet colour with concentrated sulphuric acid.

The dihydrochloride [crystals (*b*) above] was cautiously decomposed with sodium carbonate or ammonia at about 60°, the resulting base crystallised from toluene–light petroleum in minute colourless needles, m. p. 117° (Found: N, 6.5; Br, 36.0. $C_{24}H_{14}N_2Br_2$ requires N, 6.3; Br, 36.2%).

The authors are indebted to Imperial Chemical Industries Ltd., Dyestuffs Division, for various gifts.

TECHNICAL COLLEGE, HUDDERSFIELD.

[Received, December 19th, 1946.]

260. *The Replacement of the Diazonium by the Nitro-group. Part III. Decompositions by Cupro-cupri Sulphite.*

By HERBERT H. HODGSON, A. P. MAHADEVAN, and EDWARD R. WARD.

Solid aryldiazonium sulphates are first prepared and their aqueous solutions decomposed by cupro-cupri sulphite suspended in saturated aqueous sodium nitrite, yields up to 65% of nitro-compound being obtained. The precipitate obtained by addition of aqueous sodium sulphite to aqueous copper sulphate appears to be more efficient than the red-violet variety hitherto used. The method is useful for the preparation of rare dinitronaphthalenes of which six examples are given.

THE solid diazonium sulphates obtained by the general method of Hodgson and Mahadevan (this vol., p. 325) are readily decomposed when added either in aqueous solution or in solid form to a saturated solution of sodium nitrite containing cupro-cupri sulphite in suspension (cf. Hantzsch and Blagden, *Ber.*, 1900, 33, 2544; Contardi, *Annali Chim. Appl.*, 1923, 7, 13) to give excellent yields of the corresponding nitro-compounds. In particular, the method has proved to be exceedingly serviceable for obtaining the rarer dinitronaphthalenes in excellent yield and purity, and has also worked satisfactorily with benzidine, 3:3'-dinitrobenzidine, and 3:5-dinitro-*p*-toluidine. The cupro-cupri sulphite used was prepared by the addition of aqueous sodium sulphite to an equivalent amount of aqueous copper sulphate, and the greenish yellow-brown gelatinous precipitate, when washed free from excess of either component, was stirred as a slurry into the saturated aqueous sodium nitrite. So prepared, this variety of cupro-cupri sulphite appeared to be more efficient than the red-violet crystalline precipitate obtained by the addition of aqueous ammonium sulphite saturated with sulphur dioxide to warm aqueous copper sulphate and raising the temperature to 90° for 10 minutes (Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry", Vol. X, pp. 273–277).

The preparation of some solid diazonium sulphates (e.g., that from 3-nitro-*p*-toluidine) involves the use of minimum amounts of acetic and sulphuric acids, and for this purpose the inverted diazotisation procedure of Hodgson and Walker (cf. Hodgson and Turner, *J.*, 1943, 86) has been used, *viz.*, a solution of the amine in the minimum amount of concentrated sulphuric acid is treated with solid sodium nitrite and the mixture stirred into glacial acetic acid; with 3-nitro- and 3 : 5-dinitro-*p*-toluidine, the temperature could safely be allowed to reach 40° during the addition of the sodium nitrite without loss of yield of the resulting diazonium salt.

Usually, the solid diazonium sulphate, after precipitation by ether from the diazotisation medium, is dissolved in water at 0° before the cupro-cupri sulphite treatment, but it is essential first to remove admixed acid from it by washing with alcohol or ether or both. When these precautions are observed, 2-nitro-1- and 1-nitro-2-naphthylamine, which require the glacial acetic-sulphuric acid method (Hodgson and Walker, *J.*, 1933, 1620) for their diazotisation, afford the respective diazonium sulphates, the former of which readily dissolves in cold water; both form solutions which remain stable for periods of time amply sufficient for the subsequent manipulation. If, instead of first isolating the solid diazonium sulphates, the solutions of these diazonium salts as prepared by the Hodgson and Walker method (*loc. cit.*) are diluted with water and then neutralised before the cupro-cupri sulphite treatment, diazo-oxide formation occurs rapidly and no dinitronaphthalene can be obtained (cf. Veselý and Dvůrák, *Bull. Soc. chim.*, 1923, 33, 319, who failed to obtain 1 : 2-dinitronaphthalene from 1-nitro-2-naphthylamine from this cause).

The co-precipitation of sodium sulphate in almost anhydrous form with the solid diazonium sulphate probably accounts for the separation of the latter in a satisfactory crystalline state free from the stickiness usually encountered in the ordinary mode of diazonium salt isolation, since any water present will be bound by the sodium sulphate.

Addition of solid diazonium sulphate to the decomposition medium is not usually satisfactory, owing to formation of tar, probably because of local overheating during decomposition, while the tendency for hydroxylic by-products (phenols or naphthols as indicated by dissolution in alkalis), or small amounts of azo-compounds (as indicated by colour reactions) is enhanced.

It has been found that aryldiazonium cobaltinitrites (cf. Hodgson and Marsden, *J.*, 1944, 22) can be satisfactorily decomposed by adding them in aqueous suspension to the aqueous cupro-cupri sulphite-sodium nitrite mixture. Incidentally, steric hindrance appears to retard the formation of diazonium cobaltinitrites, for whereas tetrazotised 4 : 4'-dichloro-3 : 3'-diaminodiphenyl eventually affords an 85—90% yield of its tetrazonium cobaltinitrite, the formation is slow compared with that of tetrazotised benzidine.

It is of interest that the colours of 2-nitronaphthalene-1-diazonium sulphate and of 1-nitro-2-diazonium sulphate are yellow-orange and red-orange like those of the parent 2-nitro-1- and 1-nitro-2-naphthylamines.

Contardi and Mor (*Rend. Ist. Lomb. Sci. Lett.*, 1924, 57, 646; *Annali Chim. Appl.*, *loc. cit.*), from a study of the replacement of the diazonium by the nitro-group for more than 40 different amines, conclude that the introduction of the nitro-group is facilitated when nitro-groups or halogens are present in the nucleus of the amine, and this is in accord with the viewpoint of Hodgson, Leigh, and Turner (*J.*, 1942, 744) who postulated the ease of replacement of the diazonium group to depend on the positivity of the carbon atom to which the diazonium group is attached, *viz.*, the greater the positivity, the readier the replacement by halogens or the nitro-group, and the less the positivity, the greater the proneness to attack by anionoid water with replacement of the diazonium by the hydroxyl group and formation of phenols or naphthols. The reactivity of cupri-salts for replacement of diazonium by nitro-groups as found by Contardi *et al.*, and also by Hodgson and Marsden (*loc. cit.*) for the decomposition of aryldiazonium cobaltinitrites, is evidence which supports the interpretation of the Sandmeyer reaction given by Hodgson, Birtwell, and Walker (*J.*, 1941, 770; 1942, 720).

EXPERIMENTAL.

General Decomposition Procedure as indicated by the Preparation of 1 : 4-Dinitronaphthalene.—Powdered sodium nitrite (10 g.) was stirred into sulphuric acid (50 c.c., *d* 1.84), and the mixture treated gradually below 20° (external cooling) with a solution of 4-nitro-1-naphthylamine (10 g.) in glacial acetic acid (100 c.c.), and subsequently stirred for 20 minutes. Ether (700 c.c.) was next stirred into the solution at 0°, the mixture kept for 1 hour, the crystalline precipitate (by scratching) of 4-nitronaphthalene-1-diazonium sulphate filtered off, washed free from acid with ether, and dissolved in water (100 c.c.), and the solution stirred slowly into the mixture of cupro-cupri sulphite prepared as follows. An aqueous solution of crystallised sodium sulphite (50 g.) was stirred into one of crystallised copper sulphate (50 g.), and the greenish yellow-brown precipitate filtered off, washed with water, ground into a slurry with water, and then stirred into a mixture of sodium nitrite (100 g.) in water (400

c.c.). Decomposition was very rapid (cf. Hantzsch and Blagden, *loc. cit.*), and foam was broken periodically by addition of small amounts of ether; after 1 hour's stirring, when most of the inorganic matter has passed into the dark green solution, the precipitate of crude 1 : 4-dinitronaphthalene was filtered off, washed in the sequence, water, dilute sodium hydroxide, and water, dried, and crystallised from aqueous methyl alcohol from which it separated in pale yellow needles, m. p. 133.5° (Hodgson and Hathway, *J.*, 1945, 453, give m. p. 134°) (Found : N, 13.0. Calc. for $C_{10}H_6O_2N_2$: N, 12.8%); or, it can be purified by steam distillation, which for this compound is a rather slow process. Yield of pure 1 : 4-dinitronaphthalene, 7.5 g. (ca. 65%). Usually, where a readily volatile nitro-compound is formed, the steam method of removal is the more convenient.

Estimation of Yield of Diazonium Sulphate.—The solution of the diazonium sulphate in water was made up to a definite volume, an aliquot portion stirred into the alkaline β -naphthol, the precipitated arylazo- β -naphthol removed, washed, dried, and weighed, and the corresponding amount of aryl- or naphthyl-diazonium sulphate calculated.

Preparation of 3 : 3' : 4 : 4'-Tetranitrodiphenyl.—3 : 3'-Dinitrobenzidine (5 g.) was dissolved in sulphuric acid (25 c.c., *d* 1.84), powdered sodium nitrite (5 g.) added gradually below 40°, and the mixture stirred below 20° into glacial acetic acid (50 c.c.); after 30 minutes, ether (200 c.c.) was added at 0°, the mixture kept for 1 hour, and the precipitated solid tetrazonium sulphate filtered off and dealt with as by the general method. The crude 3 : 3' : 4 : 4'-tetranitrodiphenyl was filtered off, washed with water, dilute sodium hydroxide, and finally with water, dried, extracted with boiling toluene (250 c.c.), and the extract concentrated to 25 c.c.; 3 : 3' : 4 : 4'-tetranitrodiphenyl crystallised out, m. p. 188–190°, and separated subsequently from boiling 80% acetic acid in clusters of yellow needles, m. p. 191–193° (Ullmann and Bielecki, *Ber.*, 1901, **34**, 2129, give m. p. 186°) (Found : N, 16.9. Calc. for $C_{12}H_6O_8N_4$: N, 16.8%).

Preparation of 3 : 4 : 5-Trinitrotoluene.—Solid sodium nitrite (5 g.) was stirred into sulphuric acid (25 c.c., *d* 1.84), and 3 : 5-dinitro-*p*-toluidine (5 g.) was stirred below 40° into this mixture, which was then added gradually below 20° to glacial acetic acid (50 c.c.). After 30 minutes, ether (200 c.c.) was added at 0°, and the precipitated diazonium sulphate dealt with as above. After decomposition, the crude 3 : 4 : 5-trinitrotoluene was extracted thrice with boiling toluene (150 c.c. in all), and the extract concentrated to 15 c.c.; magnificent monoclinic needles of an almost pure product separated (1.3 g., m. p. 135°) (Körner and Contardi, *Atti R. Accad. Lincei*, 1915, [5], **24**, 892, give m. p. 137.5°) (Found : N, 18.7. Calc. for $C_7H_5O_6N_3$: N, 18.5%).

Amine taken.	Nitro-compound formed.	Yield of pure compound (%).		Remarks.
		(a) With slurry.	(b) With red-violet solid.	
β -Naphthylamine	β -Nitronaphthalene	40	30	Calc. on amine taken
"	"	57	40	Calc. on diazonium sulphate isolated
2-Nitro-1-naphthylamine	1 : 2-Dinitronaphthalene	53	—	Calc. on diazonium sulphate isolated
1-Nitro-2-naphthylamine	1 : 2-Dinitronaphthalene	15	—	Calc. on diazonium sulphate isolated
4-Nitro-1-naphthylamine	1 : 4-Dinitronaphthalene	65	—	Calc. on amine taken
5-Nitro-2-naphthylamine	1 : 6-Dinitronaphthalene	55	—	" "
8-Nitro-2-naphthylamine	1 : 7-Dinitronaphthalene	45	30–40	" "
6-Nitro-2-naphthylamine	2 : 6-Dinitronaphthalene	45	—	" "
Benzidine	4 : 4'-Dinitrodiphenyl	16	—	" "
3 : 3'-Dinitrobenzidine	3 : 3' : 4 : 4'-Tetranitrodiphenyl	55	—	" "
3 : 5-Dinitro- <i>p</i> -toluidine	3 : 4 : 5-Trinitrotoluene	25	—	" "

The authors are indebted to the Charles Brotherton Trust for a Research scholarship to E. R. W. for part of the time, to the Department of Scientific and Industrial Research for a Senior Research Award to E. R. W., to the Government of Madras for a Research Scholarship to A. P. M., and to Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD.

[Received, December 19th, 1946.]

261. The Reaction between Acetone and Ammonia : The Formation of Pyrimidine Compounds Analogous to the Aldoxans of Späth.

By R. B. BRADBURY, N. C. HANCOX, and H. H. HATT.

The reaction of acetone with ammonia can be conducted to give 90% yields of the monohydrate of 2 : 2 : 4 : 4 : 6-pentamethyl-2 : 3 : 4 : 5-tetrahydropyrimidine, which is readily dehydrated to the anhydrous base. By reduction with sodium in alcohol it gives the corresponding hexahydropyrimidine, and with aluminium amalgam an open chain primary-secondary diamine, $C_6H_{12}N_2$. The hexahydropyrimidine is hydrolysed with extreme ease to 2 : 4-diamino-2-methylpentane and acetone.

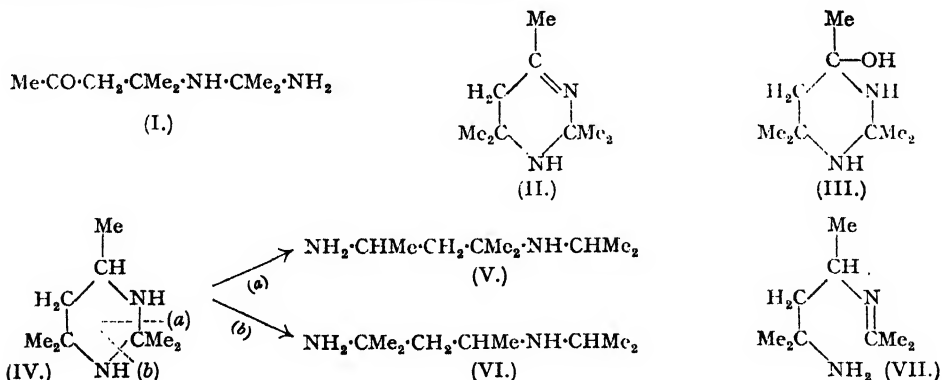
The mechanism of the formation of (II) is discussed in the light of its synthesis from mesityl oxide, acetone, and ammonia, and its quantitative hydrolysis to diacetoneamine.

Mesityl oxide and ammonia can be condensed to produce a substituted tetrahydropyrimidine analogous in structure to paralldol.

DIACETONAMINE and triacetonamine can both be obtained from the reaction of acetone with ammonia followed by acidification of the reaction products, and Heintz (*Annalen*, 1874, **174**, 133) first showed that triacetonamine was produced if the reaction mixture was heated, but that at room temperature diacetonamine was the chief product. The preparation of these compounds has since been improved by the use of calcium chloride to hasten the absorption of ammonia and to assist in the removal of water (Everest, *J.*, 1919, **115**, 588; Francis, *J.*, 1927, 2897). Further Suzuki and Horie (*Bull. Inst. Phys. Chem. Res. Japan*, 1932, **11**, 383) have found that the formation of diacetonamine was catalysed by ammonium salts, especially the nitrate and nitrite. Other compounds have been obtained from this reaction. Hock and Stuhlmann (*Ber.*, 1928, **61**, 470) by working at low temperatures isolated a compound C_9H_9ON which, as it decomposed at room temperatures into acetone and ammonia, they regarded as the initial product of the reaction analogous to aldehyde-ammonia. Patterson and McMillan (*J.*, 1921, **119**, 267) found that after a protracted reaction period a compound $C_9H_{20}ON_2$ could be obtained by cooling, to which they assigned structure (I). It has not hitherto been further investigated.

We have now found that, by the use of ammonium chloride and calcium chloride as catalysts, this compound is formed in 90% yield from acetone in 24 hours. From examination of its properties we conclude that it is a hydrate of 2 : 2 : 4 : 4 : 6-pentamethyl-2 : 3 : 4 : 5-tetrahydropyrimidine (II) to which it can be readily dehydrated over sodium hydroxide or sulphuric acid, or by distillation alone or with benzene as entrainer. The anhydrous base readily absorbs water to re-form the hydrate, and the facility of these changes is evidence for the hydrate structure assigned rather than the possible alternative (III). It seems possible that (II) may be identical with the compound $C_9H_{18}N_2$ named "acetonin" by Städeler (*Annalen*, 1859, **111**, 305; Mulder, *ibid.*, 1873, **168**, 229).

The base (II) is readily hydrolysed by boiling water to mesityl oxide, acetone, and ammonia, and by oxalic acid to ammonium and diacetonamine hydrogen oxalates and acetone. The observed molecular refraction (47·8) of the anhydrous base agrees well with the value calculated for structure (II) (47·84). Further support to this structure is given by the observation that both (II) and its hydrate are reduced by sodium and alcohol to 2 : 2 : 4 : 4 : 6-pentamethylhexahydropyrimidine (IV) and that a diamine of structure (V) or (VI) is produced by the action of aluminium amalgam on (II), its hydrate, or (IV).

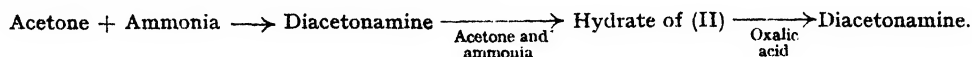


The pentamethylhexahydropyrimidine (IV) is hydrolysed more readily than the parent hexahydropyrimidine, first described by Titherley and Branch (*J.*, 1913, **103**, 330), yielding 2 : 4-diamino-2-methylpentane and acetone rapidly with dilute acids and slowly with water alone. Although it is readily converted into open chain compounds, there is no evidence for the co-existence of the Schiff's base (VII), for, unlike hexahydropyrimidine, (IV) distils without the formation of a resinous polymer and the observed molecular refraction (48·7) agrees closely with that calculated for (IV) (48·77).

Ease of ring fission in the methyl-substituted hydropyrimidines doubtless accounts in part for failure to prepare acyl derivatives, which the presence of imino- and hydroxyl groups in (II), (III), and (IV) suggests as possible. Titherley and Branch (*loc. cit.*) obtained the dibenzoyl derivative of hexahydropyrimidine by normal Schotten-Baumann procedure, but from (II) and its hydrate we obtained only *N*-benzoyldiacetonamine and from (IV) only 2 : 4-dibenzamido-2-

methylpentane. 4 : 4 : 6-Trimethylhexahydropyrimidine has been synthesised and shows intermediate properties, giving a little of its *dibenzoyl* derivative together with much 2 : 4-dibenzamido-2-methylpentane. Failure to acylate can be viewed as evidence for the hydrate structure rather than (III), for the imino-group in (II) is sterically almost identically placed with the imino-group of triacetoneamine, which forms a hydrate and a nitroso-derivative, but so far has not been benzoylated. Actually (II) reacts with nitrous acid and gives a compound of the expected composition, $C_6H_{17}ON_3$, but the yield is small and the properties are abnormal.

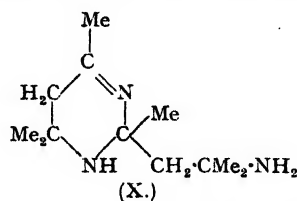
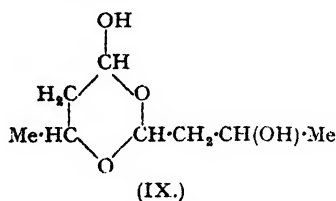
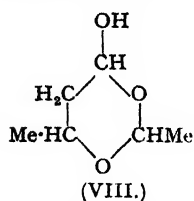
The hydrate of (II) can be synthesised from mesityl oxide, acetone, and ammonia, thus reversing the hydrolysis with acids and suggesting that formation from acetone proceeds by way of diacetoneamine and not through the hypothetical intermediate, $CMe_2(NH_2) \cdot CMe_2 \cdot OH$, proposed by Patterson and McMillan. The preparation of diacetoneamine from acetone and ammonia by the method of Everest therefore involves the formation of the hydrate, followed by its hydrolysis with oxalic acid, the scheme being :



Presumably (II) is also an intermediate in the formation of triacetoneamine.

The strong catalytic action of ammonium salts in the formation of (II) can be attributed to their acidic character in a mixture of acetone and ammonia. In support of this view, trimethylammonium chloride, which can still donate a proton, exhibits a like powerful catalytic action, whereas tetramethylammonium chloride, being unable to react in this way, has an action even weaker than calcium chloride. These catalytic effects must apply mainly to the initial formation of diacetoneamine, for the hydrate of (II) is formed readily from diacetoneamine, acetone, and ammonia in absence of a catalyst.

An analogy is apparent between the suggested mechanism for the reaction between acetone and ammonia and that given by Späth for the formation of aldoxan (VIII) by condensation of acetaldehyde (*Ber.*, 1943, 76, 57). The reaction between mesityl oxide and ammonia provides a further analogy. When the ammonia used is in excess of that needed to form diacetoneamine, a compound of the formula $C_{12}H_{25}N_3$ forms slowly. To this is assigned structure (X), closely analogous to the structure (IX) determined by Späth for paralldol. Like the substituted



tetrahydropyrimidine (II), this 2 : 4 : 4 : 6-tetramethyl-2-(2-aminoisobutyl)-2 : 3 : 4 : 5-tetrahydropyrimidine is readily reduced to the corresponding substituted hexahydropyrimidine. It forms no hydrate, but, like (II), is unstable in the presence of acids, which cause reversal of the above synthesis and give ammonium and diacetoneamine hydrogen oxalates as the chief products of decomposition.

Diaceetonamine is conveniently prepared from the hydrate of (II), a yield of 93% being obtained by boiling with alcoholic oxalic acid. This represents a yield of 56% based on the acetone used to make the hydrate and compares favourably with the 37–42% reported by Everest (*loc. cit.*), in which allowance was made for recovered acetone, and with the 70–75% yields from mesityl oxide (*Org. Synth.*, VI, 28; Smith and Adkins, *J. Amer. Chem. Soc.*, 1938, 60, 407). The synthesis of 2 : 4-diamino-2-methylpentane from acetone through the hydrate of (II) and (IV) comprises three steps all with yields exceeding 80%, and is preferable to the preparation from acetone proceeding through mesityl oxide, diacetoneamine, and its oxime.

EXPERIMENTAL.

(All melting points are corrected.)

2 : 2 : 4 : 4 : 6-Pentamethyl-2 : 3 : 4 : 5-tetrahydropyrimidine Hydrate.—(a) Acetone (290 g., 5 mol.), calcium chloride ("A.R. dried", 40 g.), and ammonium chloride (10 g.) were cooled in an autoclave to -40° , and liquid ammonia (110 g., 6.5 mol.) was added. After 24 hours' stirring at room temperature, the solid product was melted by gentle warming (40°), and the top layer separated, allowed to solidify,

and dried on porous plates (yield, 252 g.; 88%). This material is almost pure, but the small amounts of ammonium and calcium chlorides present can be removed by crystallisation from ether.

The amounts of ammonia, ammonium chloride, and calcium chloride stated above are the least for a good yield, and the use of larger amounts does not perceptibly affect the yield. When the reaction time is prolonged to 3 days the yield is increased by 1–2%.

With acetone and ammonia alone the reaction mixture remains liquid for months, although some hydrate is formed and crystallises out on cooling to -40° . Thus after 7 days a 17% yield is obtained. In presence of ammonium chloride the hydrate forms rapidly, but the solid reaction product does not separate into two layers when melted, and removal of ammonium chloride requires extraction with ether. With calcium chloride alone the yield is smaller even with a longer reaction period. The product, however, forms two liquids; the lower, containing the calcium chloride and water, is easily removed, and the upper when cooled to -40° , deposits the hydrate. The presence of small amounts of lime in the calcium chloride does not affect the yield. The presence of water is beneficial; thus fused calcium chloride alone and with half its weight of water gave yields of 55 and 65% respectively.

The table summarises the results of experiments in which 290 g. (5 mols.) of acetone and 110 g. (6.5 mols.) of ammonia were used. The reaction took place at room temperatures and the amount of catalyst used was always equivalent to 10 g. of ammonium chloride.

Catalyst.	Calcium chloride (g.).	Time (days).	Yield of (II) (%).	Catalyst.	Calcium chloride (g.).	Time (days).	Yield of (II) (%).
None.....	None	7	17	NHMe ₂ Cl	40	1	85
"	40	4	65–70	NMe ₄ Cl	40	1	35
NH ₄ Cl	none	4	70	NMe ₄ Br	40	4	66
"	40	1	88	NHMe ₂ Cl	none	4	63
NH ₄ NO ₃	40	1	85	NMe ₄ Cl *	"	4	35
NH ₄ Br	40	1	85				

* Added as a 55% aqueous solution.

(b) Mesityl oxide (120 g., 1.2 mol.) and ammonia (26 g., 1.5 mol.) were placed in an autoclave cooled to -40° and stirred for 3 days at room temperature. The mixture was again cooled, acetone (71 g., 1.2 mol.) and ammonia (40 g., 2.4 mol.) were added and the stirring was continued for 4 days. The solid hydrate of (II) was purified by crystallisation from ether (yield, 139 g.; 66%).

The hydrate when freshly crystallised from ether forms colourless crystals, m. p. $43-44^{\circ}$ [Found: C, 62.4; H, 11.5; N, 16.3; H₂O (by Dean-Stark), 10.5; equiv. (titration), 87. C₉H₁₂N₂·H₂O requires C, 62.7; H, 11.7; N, 16.3; H₂O, 10.5%; equiv., 86]. In air it slowly becomes yellow and decomposes, liberating ammonia, but it can be kept for a considerable time in a stoppered vessel in a refrigerator. It is extremely volatile and sublimes to give large, well-formed crystals of hexagonal habit. It is soluble in cold water (70 g. per 100 ml.), in cold ether (19 g. per 100 ml.), and in most organic solvents.

The oxalate was prepared from equimolecular quantities of the hydrate (II) and anhydrous oxalic acid in ether (Found: C, 44.5; H, 7.1; N, 8.0. C₉H₂₀ON₂·2H₂C₂O₄ requires C, 44.3; H, 6.8; N, 8.0%).

When to the hydrate (II) and an equivalent amount of aqueous sodium nitrite at 0° , two equivalents of 2N-hydrochloric acid were added, reaction occurred with deposition of a colourless crystalline substance during 3 hours (yield, 10–15%), m. p. $168-170^{\circ}$ (decomp.) (from acetone). The low yield, high m. p., and decomposition with dilute mineral acid without liberation of nitrous acid conflict with the supposition that it is the nitroso-derivative of (II), although the analytical data are in agreement. Molecular weight determinations gave double the expected values [Found: C, 59.2; H, 8.8; N, 22.8; M (in nitrobenzene), 371. C₉H₁₇ON₂ requires C, 59.0; H, 9.3; N, 23.0%; M, 183].

Diacetonamine Hydrogen Oxalate.—The crude hydrate of (II) (269 g.) prepared from acetone (290 g.) was dissolved in alcohol (300 ml.). An aliquot (5 ml.) was titrated with oxalic acid to determine the amount required (twice that needed for neutralisation: 365 g.). In the titration it is necessary to add about 3/4ths of the estimated amount of acid and then to warm to 80° for a few minutes to complete the hydrolysis of the hydrate. Titration at room temperature as directed by Everest gives low results and leads to the use of insufficient oxalic acid. The oxalic acid was dissolved in alcohol (2000 ml.), stirred vigorously, and the solution of the hydrate added in $\frac{1}{2}$ hour at 30° or less. After a further $\frac{1}{2}$ hour, 100 ml. of the solvent were removed and the ammonium hydrogen oxalate was filtered from the hot solution and extracted thrice with 300 ml. portions of boiling alcohol. The combined filtrates were cooled rapidly, and after 3 hours the diacetonamine hydrogen oxalate was collected and dried (m. p. $123-125^{\circ}$). The mother liquors, on evaporation, yielded a further 20 g. Yield, 309 g.; 56% based on the acetone taken. The maximum yield on this basis is 66.7%.

2 : 2 : 4 : 4 : 6-Pentamethyl-2 : 3 : 4 : 5-tetrahydropyrimidine (II).—Distillation of the hydrate under reduced pressure or dehydration using benzene as an entrainer, gives a liquid from which the base (II) is obtained by fractionation under reduced pressure (yield, 80%), b. p., 171° (decomp.)/774 mm., $55^{\circ}/10$ mm., $85^{\circ}/50$ mm.; d_{40}^{20} 0.8769; n_D^{20} 1.4561; $[R_L]_D$ 47.8 (Calc., 47.84) (Found: C, 70.3; H, 11.3; N, 18.5; equiv., 77. C₉H₁₈N₂ requires C, 70.1; H, 11.7; N, 18.2%; equiv., 77). The liquid is pale yellow and of ammoniacal odour. Addition of water to (II) gave the hydrate in 72% yield. There is some decomposition during the formation of (II), the water removed is strongly ammoniacal, and materials boiling higher than (II) are formed.

Both bases are readily decomposed in aqueous solution. The hydrate (1.72 g.) when boiled with an aqueous solution of oxalic acid (2.52 g.), the water removed on a steam-bath under slightly reduced pressure, and the dry residue extracted with absolute alcohol left ammonium hydrogen oxalate (1.03 g.; theory, 1.07 g.). The alcoholic solution on evaporation gave crude diacetonamine hydrogen oxalate, m. p., 124° , after crystallisation. In another experiment 1.72 g. were boiled with excess of aqueous oxalic acid and the acetone distilling was absorbed in water and estimated by the method of Messenger (Found: 0.57 g. Calc.: 0.58 g.). Attempts were made to benzoylate the hydrate by normal

Schotten-Baumann procedure, in dry pyridine, and in ether in presence of potassium carbonate. The only products identified were benzamide and *N*-benzoyldiacetonamine [m. p. (from alcohol) and mixed m. p. 99–100°].

2 : 2 : 4 : 4 : 6-Pentamethylhexahydropyrimidine (IV).—The hydrate (86 g.) was reduced with sodium (40 g.) in alcohol (250 ml.) and the product was first distilled with the alcohol and then separated by fractional distillation. The pure product (64 g., 82%) was colourless fuming liquid of sweet, slightly ammoniacal odour. It absorbs carbon dioxide from air and is hygroscopic; b. p., 56.5°/10 mm., 90.5°/50 mm., 172–175° (decomp.)/765 mm.; d_{25}^{25} 0.8653, n_D^{25} 1.4517; $[R_L]_D$ 48.7 [Calc. for (IV), 48.77; for (VII), 49.86] (Found: C, 69.3; H, 12.8; N, 18.2; equiv., 77. $C_8H_{20}N_2$ requires C, 69.3; H, 12.8; N, 18.0%; equiv., 78). Reduction of (II) also yields (IV), but preparation from the hydrate is preferable. Hydrolysis of (IV) with hot water is rapid and in an hour 80% of the calculated amount of acetone was liberated.

Conversion of (IV) into 2 : 4-Diamino-2-methylpentane (XI).—(IV) (54 g.) was added slowly to 2*N*-hydrochloric acid (380 ml.) at 0°, and after a day at room temperature the mixture was heated to remove acetone. Sufficient solid sodium hydroxide was added to give a 40% aqueous solution, the diamine layer was separated, and the aqueous liquors were extracted with ether. The diamine was dried over potassium hydroxide and barium oxide. Fractional distillation gave a colourless liquid (yield, 33.5 g.; 83%), b. p. 45–46°/10 mm.; d_{25}^{25} 0.8312; n_D^{25} 1.4386; $[R_L]_D$ 36.8 (Calc., 36.75) (Found: C, 62.6; H, 13.5; N, 23.1. $C_6H_{14}N_2$ requires C, 62.1; H, 13.8; N, 24.1%). (XI) was also prepared from diacetanamine by the method of Harries and Adamiantz (*Ber.*, 1901, 34, 301); b. p. 42–46/10 mm.; n_D^{25} 1.439; d_{25}^{25} 0.836.

The diacetyl derivative obtained from (XI) and either acetic anhydride or keten formed colourless crystals from chloroform, m. p., 163° (Found: C, 60.0; H, 10.0; N, 14.2. $C_{10}H_{20}O_4N_2$ requires C, 60.0; H, 10.0; N, 14.0%). The dibenzoyl derivative obtained by the Schotten-Baumann procedure from (XI) formed colourless rosettes from alcohol, m. p., 153° (Found: C, 74.2; H, 7.4; N, 8.7. $C_{20}H_{24}O_4N_2$ requires C, 74.1; H, 7.4; N, 8.6%); it showed no depression of melting point with the derivative prepared from the specimen of (XI) synthesised from diacetanamine. This same dibenzoyl derivative is slowly formed when (IV) is benzoylated.

2 : 4-Diamino-2-methylpentane (XI), chloro-2 : 4-dinitrobenzene, sodium acetate, and alcohol were refluxed for 1 hour. The *bis*-2 : 4-dinitrophenyl derivative formed yellow crystals from *o*-dichlorobenzene, m. p., 235° (Found: C, 48.3; H, 4.4; N, 18.9. $C_{18}H_{20}O_4N_4$ requires C, 48.2; H, 4.5; N, 18.7%). With like experimental conditions (IV) gave this same compound.

2-Keto-4 : 4 : 6-trimethylhexahydropyrimidine.—Equimolecular amounts of 2 : 4-diamino-2-methylpentane and urea were heated at 150° for 1 hour. The product separated from acetone as white crystals, m. p. 205–206° (Found: C, 59.5; H, 9.7; N, 19.9. $C_7H_{14}ON_2$ requires C, 59.2; H, 9.9; N, 19.7%).

4 : 4 : 6-Trimethylhexahydropyrimidine (XII).—The method used by Titherley and Branch (*J.*, 1913, 103, 334) for hexahydropyrimidine was adopted, and 2 : 4-diamino-2-methylpentane (XI) (2.09 g.) was neutralised with 0.2*N*-hydrochloric acid, an equal weight of (XI) added, followed by 36% aqueous formaldehyde (3.5 ml.) in 3 hours. After a further 2 hours, potassium hydroxide (60 g.) was added, the product extracted with ether, and the solution dried (BaO) and distilled. Yield, 3.3 g.; b. p. 55–57°/10 mm.; n_D^{25} 1.457 (Found: C, 65.7; H, 12.8; N, 21.7; equiv., 132. $C_7H_{14}N_2$ requires C, 65.7; H, 12.5; N, 21.9%; equiv. (monoacid), 128).

Trimethylhexahydropyrimidine (XII), by Schotten-Baumann procedure, gave its own *NN'*-dibenzoyl derivative, together with 2 : 4-dibenzamido-2-methylpentane. The former being the more soluble, only a partial separation was made by fractional crystallisation from alcohol, and the final separation was made by hand picking. This dibenzoyl derivative forms needles, m. p. 156° (Found: C, 75.0; H, 6.9; N, 8.3. $C_{21}H_{24}O_4N_2$ requires C, 74.8; H, 7.1; N, 8.3%).

2 (or 4)-Amino-4 (or 2)-isopropylamino-2-methylpentane (V) or (VI).—This was obtained by reduction of (II), its hydrate, or (IV) with an equal weight of aluminium amalgam in moist ether. The reaction proceeded slowly and was complete after 2 days; the ethereal liquors were then filtered off, and the oxide sludge was washed with ether. When distilling the ethereal liquors the alcohol introduced with the amalgam distilled as a fore-fraction containing much diamine. Yields of pure diamine were 60–70% when this fore-fraction was neglected; with recovery from it the yields rose to 85%. Dried over sodium, (VI) forms a colourless hygroscopic liquid, b. p. 178°/760 mm. (no decomp.), 65–67°/10 mm., 104°/65 mm.; d_{25}^{25} 0.8130; n_D^{25} 1.432 (Found: C, 68.4; H, 14.0; N, 17.7; equiv., 81. $C_9H_{22}N_2$ requires C, 68.4; H, 13.9; N, 17.7%; equiv., 79).

The dihydrochloride, prepared in dry ether and crystallised from amyl alcohol, had m. p. 250° (decomp.) (Found: Cl, 30.5. $C_9H_{22}N_2 \cdot 2HCl$ requires 30.7%). The dibenzoyl derivative was prepared by the Schotten-Baumann method; crystals from alcohol, m. p. 133° (Found: C, 75.2; H, 8.25; N, 7.8. $C_{23}H_{26}O_4N_2$ requires C, 75.4; H, 8.2; N, 7.6%).

Sufficient chloro-2 : 4-dinitrobenzene was used with sodium acetate in alcohol to substitute both amino-groups, but only one reacted. The 2 : 4-dinitrophenyl derivative crystallised from alcohol in orange needles, m. p. 91° (Found: C, 55.6; H, 7.4; N, 17.7. $C_{18}H_{20}O_4N_4$ requires C, 55.6; H, 7.4; N, 17.3%).

2 : 4 : 4 : 6-Tetramethyl-2-(2-aminoisobutyl)-2 : 3 : 4 : 5-tetrahydropyrimidine (X).—Mesityl oxide (120 g.) and liquid ammonia (49 g.) were cooled in an autoclave to –40° and then stirred for 24 hours at room temperature. The autoclave was then cooled again and a further quantity of mesityl oxide (120 g.) and ammonia (26 g.) added. After 6 days at room temperature, the product was removed and cooled to –40°. The white crystalline solid that separated (58 g.) crystallised from ether in white flakes, m. p. 61–62° (Found: C, 68.0; H, 11.5; N, 19.9; equiv., 71; *M* (in nitrobenzene), 218. $C_{15}H_{22}N_2$ requires C, 68.2; H, 11.8; N, 19.9%; equiv., 70.3; *M*, 211).

This compound (X) reacts rapidly with a cold solution of oxalic acid in alcohol, a precipitate of ammonium hydrogen oxalate appearing shortly after the reagents are mixed. From (X) (2.11 g.) and oxalic acid hydrate (3.78 g.) in alcohol (10 ml.) after $\frac{1}{2}$ hour at the b. p., filtration gave ammonium hydrogen oxalate (1.8 g.) and concentration of the filtrate diacetanamine hydrogen oxalate (0.87 g.).

The latter melted at 124–125° after crystallisation (Found: C, 43.0; H, 7.8. Calc. for $C_8H_{17}O_6N$: C, 43.0; H, 7.6%). There were 2.1 g. of uncrystallisable residues.

2:4:4:6-Tetramethyl-2-(2-aminoisobutyl)hexahydropyrimidine.—Reduction of (X) (21 g.) in alcohol (100 ml.) with sodium (10 g.) followed by the addition of water (50 ml.) gave the product as an oil, which was dried and fractionally distilled (yield, 12–14 g.). It was a colourless liquid, b. p. 122–125°/10 mm.; d_{20}^{25} 0.8668; n_D^{25} 1.458 (Found: C, 67.4; H, 13.0; N, 20.1; equiv., 72. $C_{13}H_{27}N_3$ requires C, 67.6; H, 12.7; N, 19.7%; equiv., 71).

We wish to thank Mr. D. J. Clark, M.Sc., of these laboratories, for the micro-analyses.

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[Received, December 19th, 1946.]

262. The Structure of Glycogen. Ratio of Non-terminal to Terminal Glucose Residues.

By T. G. HALSALL, E. L. HIRST, and J. K. N. JONES.

An assay of the proportion of terminal groups present in various glycogens has been made by measuring the amount of formic acid liberated on oxidation of the polysaccharide by potassium periodate. All the glycogens examined gave results indicating that approximately 12 glucose residues were present per end group, except that certain samples of rabbit-liver glycogen contained approximately 18 residues per end group. The results are in agreement with determinations of the percentage of end groups arrived at by estimation of the tetramethyl glucose produced on hydrolysis of the methylated glycogen.

THE proportion of terminal groups present in samples of glycogen isolated from various sources has been determined previously by methylation of the polysaccharide followed by the quantitative determination of the amount of tetramethyl methyl-*d*-glucoside in the products of methanolysis of the methylated polysaccharide, and in this way it was found that for most samples the ratio of terminal to non-terminal glucose residues was approximately 1 to 12. Nevertheless, in certain samples of rabbit-liver glycogen the ratio was nearer 1 to 18. No completely satisfactory explanation of this variation has yet been put forward, and further investigation was clearly needed. The examination of a large number of samples by the classical methylation technique is a lengthy operation, but starches and glycogens respond readily to the periodic acid oxidation process in which, under carefully standardised conditions, formic acid is liberated quantitatively from the terminal residues of each side chain, and it was decided, therefore, to examine various samples of glycogen by this method (cf. Brown, Dunstan, Halsall, Hirst, and Jones, *Nature*, 1945, 156, 785; *idem*, *J.*, in the press). In some instances comparative experiments were made by the methylation method, using newly developed semi-micro-methods for the determination of the tetramethyl methylglucoside which arises from each end group (Bell, *J.*, 1944, 473; Jones, *J.*, 1944, 333; Brown and Jones, in the press).

Through the kindness of Dr. D. J. Bell of Cambridge University, we were able to investigate numerous samples of glycogens which he had isolated from various sources. These included glycogen from *Ascaris lumbricoides*, *Mytilus edulis*, human muscle, rabbit liver, rabbit muscle (fasted), and horse muscle. Some of these had already been assayed by him using the methylation procedure. A check was thus provided of the results derived by determination of the formic acid produced after oxidation of the glycogen with potassium periodate. Figures in excellent agreement with those obtained by the use of the methylation procedure were observed. Dr. F. Smith very kindly placed at our disposal samples of guinea-pig-liver glycogen and rabbit-liver glycogen which had been assayed by the methylation technique at Birmingham University.

The proportion of end groups in rabbit-liver glycogen was first determined by Haworth and Percival (*J.*, 1932, 2277) who reported the figure of 1 for every 12 glucose residues. Examination of another sample of rabbit-liver glycogen by Haworth, Hirst, and Isherwood (*J.*, 1937, 577) showed, however, that this glycogen contained approximately 18 glucose residues per end group. This result was confirmed by Bell (*Biochem. J.*, 1936, 30, 1612) and by Bacon, Baldwin, and Bell (*ibid.*, 1944, 38, 198) who demonstrated that the ratio of terminal to non-terminal residues in rabbit-liver glycogen may be either 12 to 1 or 18 to 1 approximately, the value observed being apparently dependent upon the carbohydrate diet of the rabbit. We have now confirmed by the periodate oxidation method the higher figure for the sample of rabbit-liver glycogen examined by Haworth, Hirst, and Isherwood, and have obtained also a ratio of 18 to 1 approximately, by both methods of assay, for another sample of rabbit-liver glycogen prepared

by Messrs. Hopkin & Williams Ltd. On the other hand, the sample of rabbit-liver glycogen which had been found by Bell to give the value 12 gave a low value by the periodate method also. Further investigation is clearly required to ascertain the precise reasons for these unpredictable variations which appear to occur only in rabbit-liver glycogen. In all other cases, including those cited in the table and the numerous samples of fish-liver and fish-muscle glycogen examined by Smith (*J.*, 1939, 1915), the value obtained has been 12 approximately.

EXPERIMENTAL

Potassium Periodate Oxidation of Glycogens. General Procedure.—The glycogen (*ca.* 500 mg.) was placed in a 500 ml. stoppered bottle which had been cleaned with chromic acid and steamed out. A known volume of water was added, followed by potassium chloride (5 g.) and a known excess of an aqueous solution of sodium metaperiodate. The oxidations were carried out at 15° with continuous shaking and in dim light (sunlight must be avoided). Portions of the solution (20 ml.) were withdrawn at intervals, excess of ethylene glycol was added, and the formic acid present was estimated by titration with 0.1*N*-barium hydroxide using a micro-burette and methyl-red as indicator. The resulting titres, after correction when necessary to allow for the slight acidity or alkalinity of the glycogen, were plotted against time to make sure that the normal type of reaction was proceeding, and the acid titre corresponding to 150 hours was used in the calculations, this being the time required for the liberation of 1 mol. of formic acid from β -methyl-*D*-maltoide under these conditions (Halsall, Hirst, and Jones, *J.*, *loc. cit.*). From this titre the size of the repeating unit was calculated. The results are given in the table.

Source of glycogen.	Wt. of glycogen (mg.).	Yield of formic acid (mg.).	Glucose residues per end group.	
			(a) By periodate method.	(b) By methylation method.
1. <i>Ascaris lumbricoides</i>	567	13.5	12	13—14 (a)
2. <i>Mytilus edulis</i>	510	14.1	10	11 (b)
3. Human muscle	518.8	12.9	11	—
4. Rabbit (fasted) muscle	510.5	11.0	13	—
5. Horse muscle	400.4	8.1	14	12 (c)
6. Rabbit liver	365.5	7.2	14	12 (d)
7. Rabbit liver	509	9.0	16	18 (e)
8. Rabbit liver	871	13.8	18	18 (f)
9. Rabbit liver	216	4.2	14	12 (g)
10. Guinea-pig liver	174.5	3.9	13	12 (g)

Glycogens 1—6 were prepared by Dr. D. J. Bell.

Glycogen 7 was a sample of the material used by Haworth, Hirst, and Isherwood (*loc. cit.*).

Glycogen 8 was prepared by Messrs. Hopkin & Williams, Ltd.

Glycogens 9 and 10 were prepared by Dr. F. Smith.

(a) Bell, *J.*, 1944, 474.

(b) This figure was obtained for another sample examined by Meyer, *Naturwiss.*, 1941, 29, 287.

(c) Bell, *Biochem. J.*, 1935, 29, 2031.

(d) Bell, *Biochem. J.*, 1937, 31, 1683.

(e) Haworth, Hirst, and Isherwood (*loc. cit.*).

(f) Present paper.

(g) F. Smith (private communication).

Size of Repeating Unit of Rabbit-liver Glycogen (No. 8 in Table), by the Methylation Method.—The glycogen was methylated with methyl sulphate and sodium hydroxide according to the method of Hirst and Young (*J.*, 1939, 1471). The methylated glycogen [759.5 mg.; $[\alpha]_D^{25} + 206^\circ$ in chloroform (*c.* 8.5); OMe, 45.1%] was hydrolysed with methyl-alcoholic hydrogen chloride (1.5%; 100 ml.) and the amount of 2:3:4:6-tetramethyl methylglucoside in the resulting mixture of glucosides was estimated by the partition method of Brown and Jones (this vol., p. 1344). Yield of 2:3:4:6-tetramethyl methylglucoside, 50.3 mg.; $n_D^{18} 1.4445$; $[\alpha]_D^{25} + 66^\circ$ in water (*c.* 2.3); corresponding to the presence of 18—19 glucose residues per end group.

We wish to thank Mr. L. Hough for assistance in the experimental work, and one of us (T. G. H.) wishes to thank the British Cotton Industry Research Association for the award of a Shirley Research Fellowship.

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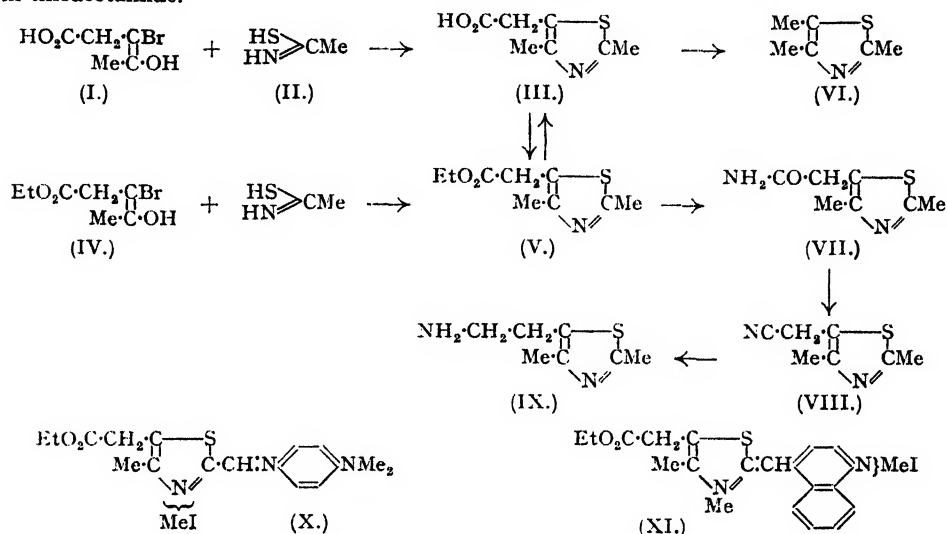
[Received, December 23rd, 1946.]

263. The Conversion of Sucrose into Thiazole Derivatives. Part II. 2:4-Dimethylthiazole Derivatives and 2:4:5-Trimethylthiazole.

By HILDA GREGORY and L. F. WIGGINS.

Condensation of β -bromolævulinic acid and its ethyl ester with thioacetamide yields 2:4-dimethylthiazole-5-acetic acid and ethyl 2:4-dimethylthiazole-5-acetate respectively. Several derivatives of the latter product are described, and decarboxylation of 2:4-dimethylthiazole-5-acetic acid affords a convenient method for the preparation of 2:4:5-trimethylthiazole.

SUCROSE can be readily transformed into lævulic acid, and in Part I (this vol., p. 590) we described several sulphanilamidothiazoles, which were obtained through the condensation of β -bromolævulic acid and its ethyl ester with thiourea. Continuing this theme, we have now investigated the condensation of β -bromolævulic acid (I) with thioacetamide (II), whereby 2:4-dimethylthiazole-5-acetic acid hydrobromide is obtained; this is readily converted into 2:4-dimethylthiazole-5-acetic acid (III). The latter, on esterification, gave ethyl 2:4-dimethylthiazole-5-acetate (V), identical with the product of the condensation of ethyl β -bromolævulate (IV) with thioacetamide.



Decarboxylation of 2:4-dimethylthiazole-5-acetic acid was effected smoothly to give an 80% yield of 2:4:5-trimethylthiazole (VI). Hitherto, this trimethylthiazole has only been prepared by the condensation of thioacetamide with methyl 1-chloroethyl ketone (Roubleff, *Annalen*, 1890, 259, 258).

Treatment of the thiazole ester with concentrated aqueous ammonia gave the corresponding amide (VII) which was readily dehydrated with phosphorus oxychloride to 2:4-dimethyl-5-cyanomethylthiazole (VIII). The latter, on catalytic hydrogenation over Raney nickel, was converted into 2:4-dimethyl-5-2'-aminoethylthiazole (IX) which, however, was unstable and could only be isolated as the *dipicrate*. In view of the previous work of Hinegardner and Johnson (*J. Amer. Chem. Soc.*, 1930, 52, 3724), this compound should exhibit some physiological activity as a sympathomimetic agent.

It has been shown previously by Mills and Smith (*J.*, 1922, 121 2724) that the activity of the substituent methyl group in the thiazole ring depends upon its position. Thus, whereas 4-phenyl-2-methylthiazole will condense readily with benzaldehyde and phthalic anhydride, and its quaternary ammonium salts couple with *p*-dimethylaminobenzaldehyde, its isomer, 2-phenyl-4-methylthiazole, undergoes none of these reactions. In this work we found that ethyl 2:4-dimethylthiazole-5-acetate methiodide underwent reaction with only 1 mole of *p*-nitrosodimethylaniline to form 4-methyl-5-carbethoxymethylthiazole-2-aldehyde *p*-dimethylaminoanil methiodide (X) which was a brownish-green crystalline compound with a bluish-green metallic reflex, giving rise to deep purple aqueous solutions. Similarly, ethyl 2:4-dimethylthiazole-5-acetate methiodide condensed with 1 mole of quinoline methiodide to give a deep red crystalline compound which, by analogy to 4-phenyl-3-methyl-2-thiazolonyl-4-quinolymethane methiodide of Mills and Smith (*loc. cit.*), must be 3:4-dimethyl-5-carbethoxymethyl-2-thiazolonyl-4-quinolymethane methiodide (XI).

EXPERIMENTAL.

Ethyl 2:4-Dimethylthiazole-5-acetate.—To ethyl β -bromolævulate (20.8 g.) dissolved in ethyl alcohol (20 c.c.), thioacetamide (7.0 g.) was slowly added in small portions; an exothermic reaction occurred with formation of a yellow solution. After 12 hours at room temperature, the alcohol was removed and the thick yellow syrup thus obtained dissolved in water, a few drops of hydrochloric acid (5*N*) were added, and the solution was extracted with ether to remove any unchanged starting materials. Ammonia (5*N*) was added to the aqueous solution at 0° until the solution was slightly alkaline (litmus);

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a yellow oil then separated. The crude product was extracted with ether, and the ethereal layer was washed with water and dried (MgSO_4), and the ether removed. The residual liquid was distilled in a vacuum; ethyl 2 : 4-dimethylthiazole-5-acetate was thus obtained as a pale yellow liquid, b. p. $142^\circ/15$ mm., $212^\circ/756$ mm., n_D^{20} 1.4942. Yield, 11.6 g. (82.5%) (Found : C, 53.9; H, 6.1; N, 7.2; OEt, 23.1. $\text{C}_9\text{H}_{13}\text{O}_2\text{NS}$ requires C, 54.2; H, 6.5; N, 7.0; OEt, 22.6%). The picrate was obtained as a yellow, crystalline solid, m. p. 168° (Found : C, 42.4; H, 3.4; N, 13.1. $\text{C}_{18}\text{H}_{16}\text{O}_6\text{N}_4\text{S}$ requires C, 42.1; H, 3.7; N, 13.1%).

Condensation of β -Bromolævulic Acid with Thioacetamide.—Thioacetamide (1.0 g.) was added in portions to β -bromolævulic acid (2.25 g.) at 80° . After a few minutes, an exothermic reaction occurred, and when the mixture had cooled to room temperature, a partly solid product was obtained. This was pressed on a porous pile, and colourless crystals isolated, which were recrystallised from acetone-ethyl alcohol-light petroleum (b. p. 40 – 60°). After two recrystallisations, pure 2 : 4-dimethylthiazole-5-acetic acid hydrobromide was obtained as colourless crystals, m. p. 183° . Yield, 1.78 g. (61.2%) (Found : C, 33.7; H, 4.3. $\text{C}_9\text{H}_{10}\text{O}_2\text{NBrS}$ requires C, 33.4; H, 4.0%).

The free base was obtained from the hydrobromide (1.5 g.) by dissolving it in water (6 c.c.) and heating under reflux for 15 minutes. The strongly acid solution was cooled, and a concentrated aqueous solution of potassium hydroxide added carefully, until, when the solution was still acid to litmus, crystals separated. These were filtered off and recrystallised from hot water; m. p. 185° . Yield, 0.93 g. (91.4%).

Esterification of 2 : 4-Dimethylthiazole-5-acetic Acid.—The acid (2.0 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride (50 c.c.) for 6 hours. The resulting solution was neutralised with barium carbonate, the barium salts were filtered off, and the alcoholic solution was evaporated to dryness under reduced pressure. The residue was extracted with ether, and the ethereal extract evaporated to a brown liquid which was subsequently distilled; b. p. $212^\circ/745$ mm., n_D^{20} 1.4943 (Found : OEt, 22.9. Calc. for $\text{C}_9\text{H}_{13}\text{O}_2\text{NS}$: OEt, 22.6%). Yield of ethyl 2 : 4-dimethylthiazole-5-acetate, 1.46 g. (62.7%).

2 : 4 : 5-Trimethylthiazole.—2 : 4-Dimethylthiazole-5-acetic acid (0.8 g.) was heated on an oil-bath in a distillation flask. At 190° (bath temp.) the crystals melted; at 235° (bath temp.) carbon dioxide was evolved and a colourless, pungent smelling liquid distilled, b. p. 164 – 166° (vapour temp.), n_D^{20} 1.5060. Yield of 2 : 4 : 5-trimethylthiazole, 0.49 g. (82.5%). On treatment with one mol. of picric acid, yellow needles of 2 : 4 : 5-trimethylthiazole picrate were obtained, m. p. 133 – 134° (Found : C, 40.4; H, 3.7. Calc. for $\text{C}_{12}\text{H}_{15}\text{O}_7\text{N}_3\text{S}$: C, 40.4; H, 3.4%). Roubleff (*loc. cit.*) gives m. p. 133° .

2 : 4-Dimethylthiazole-5-acetamide.—Ethyl 2 : 4-dimethylthiazole-5-acetate (1.0 g.) was suspended in concentrated ammonia solution (d 0.88; 5 c.c.), and the mixture shaken for 2 hours; a clear yellow solution was then obtained. After several hours at 0° , colourless needles separated. More crystals were obtained by concentration of the mother liquors. The total crude product recrystallised from ethyl alcohol-ether in feathery, colourless needles of 2 : 4-dimethylthiazole-5-acetamide, m. p. 173° . Yield, 0.72 g. (84.3%) (Found : C, 49.4; H, 5.5; N, 17.1. $\text{C}_7\text{H}_{10}\text{ON}_2\text{S}$ requires C, 49.4; H, 5.9; N, 16.5%). On treatment with picric acid, long needles of the picrate were obtained, m. p. 185° (Found : C, 39.4; H, 3.5; N, 17.4. $\text{C}_{13}\text{H}_{13}\text{O}_6\text{N}_3\text{S}$ requires C, 39.1; H, 3.3; N, 17.5%).

2 : 4-Dimethyl-5-cyanomethylthiazole.—2 : 4-Dimethylthiazole-5-acetamide (1.3 g.) was heated with phosphorus oxychloride (freshly distilled; 5 c.c.) on an oil-bath for 45 minutes at 105 – 115° . The phosphorus oxychloride was then removed on a water-bath at 50° under reduced pressure. To the dark syrupy residue, crushed ice was added, then solid sodium carbonate until the solution was alkaline (litmus). The dark brown solution was then exhaustively extracted with ether, the ethereal extract dried (MgSO_4), and the ether removed by evaporation. The crystalline residue was recrystallised from hot water to give needles of 2 : 4-dimethyl-5-cyanomethylthiazole, m. p. 87° . Yield, 1.0 g. (86%) (Found : C, 54.0; H, 4.9; N, 17.8. $\text{C}_7\text{H}_8\text{N}_2\text{S}$ requires C, 55.3; H, 5.2; N, 18.1%). The picrate was obtained as a yellow crystalline solid, m. p. 125° (Found : C, 40.9; H, 3.2. $\text{C}_{13}\text{H}_{11}\text{O}_7\text{N}_3\text{S}$ requires C, 40.9; H, 2.9%).

Reduction of 2 : 4-Dimethyl-5-cyanomethylthiazole.—2 : 4-Dimethyl-5-cyanomethyl thiazole (0.95 g.) was dissolved in methyl alcohol (40 c.c.) and hydrogenated over Raney nickel at room temperature. When approximately the theoretical amount of hydrogen had been absorbed and no further absorption occurred, the catalyst was filtered off and the methyl alcohol evaporated under reduced pressure in an atmosphere of nitrogen. The product decomposed on keeping but was characterised as the dipicrate. A solution of the syrup (0.2 g.) in alcohol was added to a hot concentrated aqueous solution of picric acid (0.6 g.). On cooling, an oil separated, which eventually solidified and recrystallised from hot water in yellow crystals, m. p. 169° . It was 2 : 4-dimethyl-5-2'-aminomethylthiazole dipicrate (Found : C, 37.3; H, 3.0; N, 17.9. $\text{C}_{15}\text{H}_{18}\text{O}_{14}\text{N}_6\text{S}$ requires C, 37.1; H, 2.9; N, 18.2%).

Condensation of Ethyl 2 : 4-Dimethylthiazole-5-acetate Methiodide with *p*-Nitrosodimethylaniline.—Ethyl 2 : 4-dimethylthiazole-5-acetate (1.0 g.) was kept with methyl iodide (100% excess) at room temperature for 24 hours. The methyl iodide was then evaporated under reduced pressure. A yellow oil was obtained which slowly crystallised; it recrystallised from alcohol in colourless prisms, m. p. 133° , which decomposed too rapidly for analytical figures to be obtained.

To an alcoholic solution of ethyl 2 : 4-dimethylthiazole-5-acetate methiodide (crude oil; 1.0 g.) was added an alcoholic solution of *p*-nitrosodimethylaniline (0.5 g.), whereby a bright green solution was obtained. Piperidine (2 drops) was added; the colour changed to reddish brown, and the solution was heated under reflux for 15 minutes; a purple colouration had then developed. On cooling, crystals separated and were filtered off (0.3 g.). The solution was again heated for a further 2 hours, and on cooling, more crystals were obtained (0.2 g.). The crude product was recrystallised from aqueous methyl alcohol, and 4-methyl-5-carboxymethylthiazole-2-aldehyde *p*-dimethylaminoanil methiodide was obtained as a brownish-green crystalline compound with a bluish-green metallic reflex, m. p. 208° . In dilute aqueous or alcoholic solution the crystals gave a deep purple colouration, which was easily discharged by acids and regenerated by alkali (Found : C, 45.9; H, 5.5. $\text{C}_{18}\text{H}_{24}\text{O}_2\text{N}_4\text{S}$ requires C, 45.7; H, 5.1%).

Condensation of Ethyl 2:4-Dimethylthiazole-5-acetate Methiodide with Quinoline Methiodide.—To ethyl 2:4-dimethylthiazole-5-acetate methiodide (crude oil; 1.0 g.) dissolved in ethyl alcohol (10 c.c.) was added an alcoholic solution of quinoline methiodide (1.7 g.; 100% excess) and sodium hydroxide (0.17 g.). The solution was heated under reflux for 30 minutes; a vivid red colouration had then developed. On cooling, a semi-solid product separated, which was recrystallised from methyl alcohol to give 3:4-dimethyl-5-carbomethoxymethyl-2-thiazolonyl-4-quinolylmethane methiodide as dark red crystals with a bright green, metallic reflex, m. p. 200°. Yield, 0.35 g. (Found: C, 50.3; H, 5.1; N, 6.2. $C_{20}H_{23}O_2N_2S$ requires C, 49.8; H, 4.8; N, 5.8%).

The authors wish to express their thanks to Professors W. N. Haworth, F.R.S., and J. L. Simonsen, F.R.S., for their interest, and to the Colonial Products Research Council for financial support.

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[Received, December 24th, 1946.]

264. Anhydrides of Polyhydric Alcohols. Part VII.

1:4-3:6-Dianhydro-d- and -l-Iditol.

By L. F. WIGGINS.

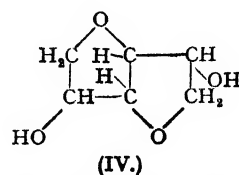
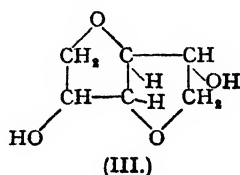
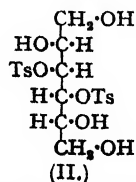
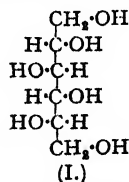
l-Iditol readily undergoes anhydride formation on being heated in the presence of hydrochloric acid, giving 1:4-3:6-dianhydro-*l*-iditol the structure of which is proved by a constitutional synthesis of its enantiomorph.

THE action of acidic reagents on both mannitol and sorbitol gives rise to the dianhydrides of these polyhydric alcohols by internal loss of two molecules of water. Dianhydromannitol, first obtained by Fauconier (*Compt. rend.*, 1882, 95, 991), was shown to possess the constitution of 1:4-3:6-dianhydromannitol by Wiggins in Part I of this series (*J.*, 1945, 4) and by Hockett, Fletcher, Sheffield, Goepf, and Soltzberg (*J. Amer. Chem. Soc.*, 1946, 68, 930). Dianhydrosorbitol, prepared in a similar way to its mannitol analogue, was shown by synthetical methods (Wiggins and Montgomery, *Nature*, 1946, 157, 372; *J.*, 1946, 390) also to have the 1:4-3:6-ring structure. Hockett, Fletcher, Sheffield, and Goepf (*J. Amer. Chem. Soc.*, 1946, 68, 927) have arrived at the same conclusions by different methods.

l-Iditol (I) also undergoes a similar dehydration on being heated in the presence of acids and gives a dianhydride, in the form of a *hemihydrate* which, like the corresponding compounds of mannitol and sorbitol, is stable to treatment with sodium methoxide at 120° under pressure. The *bismethanesulphonyl* and the *dibenzoyl* derivative were readily obtained from it.

By analogy with the dianhydrides of mannitol and sorbitol it would be expected that this compound would also have the hydrofuranol type of ring structure shown in (III). After the completion of this work, Fletcher and Goepf (*J. Amer. Chem. Soc.*, 1945, 67, 1042; 1946, 68, 939) reported that 1:4-3:6-dianhydrosorbitol and dianhydromannitol on dehydrogenation with Raney nickel followed by hydrogenation are both partly converted into dianhydroiditol, and on the assumption that the rings are stable under these conditions, have declared the establishment of the 1:4-3:6-ring structure for all three hexitol dianhydrides. The present paper is concerned with a proof of constitution of the dianhydroiditol along quite different lines. A preliminary note of this appeared in *Nature* (1946, 157, 372).

If mannitol could be tosylated at C_3 and C_4 to give 3:4-ditosyl mannitol (II), this compound on removal of the tosyl groups with sodium methoxide could form only two dianhydrides, (a) 1:3-4:6-dianhydrohexitol, and (b) 1:4-3:6-dianhydrohexitol. Moreover, since it is established in the sugar series that, when hydrolytic removal of tosyl groups is accompanied by anhydro-ring formation, Walden inversion always accompanies the hydrolysis (see Peat, *Ann. Reports*, 1939, 36, 258), it follows that both (a) and (b) would have the configuration of *d*-iditol.



A suitable derivative substituted at C_3 and C_4 with tosyl residues is 3:4-ditosyl 1:2-5:6-diacetone mannitol (Brigl and Gruner, *Ber.*, 1934, 67, 1969). This compound, on partial hydrolysis

followed by acetylation, gave liquid 3:4-ditosyl 1:2:5:6-tetra-acetyl mannitol which on treatment with sodium methoxide gave a crystalline dianhydrohexitol which gave crystalline bis-methanesulphonyl and dibenzoyl derivatives. These had the same melting points as and specific rotation equal, but opposite in sign, to the corresponding derivatives obtained from the product of the anhydroidisation of *l*-iditol. Therefore the two sets of compounds are enantiomorphous, and dianhydro-*d*-iditol and bismethanesulphonyl and dibenzoyl dianhydro-*d*-iditol must have been obtained from mannitol.

The precise constitution of dianhydroiditol is limited to the possibilities (a) and (b) above. Since (a) involves four-membered rings which are extremely unlikely of formation when five-membered rings are possible, and since in (a) the two free hydroxyl groups would approach near enough to be joined in acetal formation by a benzylidene residue, and because dianhydro-iditol does not form such a derivative, structure (b) must be regarded as the correct one. Dianhydro-*d*-iditol is formulated by (III), a representation differing from that of 1:4-3:6-dianhydro-*d*-mannitol (IV) only in the orientation of the two rings.

EXPERIMENTAL.

1-Iditol.—This was prepared from *l*-sorbose by catalytic hydrogenation and separated from the accompanying *l*-sorbitol by fractional crystallisation of the acetyl derivatives (Jones and Wiggins, *J.*, 1944, 363).

Action of Hydrochloric Acid on 1-Iditol.—Crystalline *l*-iditol (5 g.) was boiled under reflux for 50 hours with fuming hydrochloric acid (50 c.c.). The dark brown solution was evaporated to a syrup which was distilled at 150–155° (bath temp.)/0.05 mm. The distillate (3.1 g.) crystallised completely on cooling. It recrystallised in prisms from ethyl acetate (2.3 g.), m. p. 43–45°, $[\alpha]_D^{25} + 18.4^\circ$ (c, 2.389 in water), and was 1:4-3:6-dianhydro-*l*-iditol hemihydrate (Found: C, 46.7, 46.1; H, 7.0, 7.3. $C_8H_{10}O_4 \cdot \frac{1}{2}H_2O$ requires C, 46.5; H, 7.1%).

Treatment of Dianhydro-*l*-iditol with Sodium Methoxide.—The dianhydroiditol (1.7 g.) was heated in a sealed tube with 5% methyl-alcoholic sodium methoxide at 120° for 24 hours. Thereafter, the solution was diluted with water, neutralised with sulphuric acid, and evaporated to dryness, and the residue was extracted with ethyl acetate. The extract was evaporated and the syrupy product distilled at 160°/0.02 mm. The distillate, which completely crystallised, was unchanged 1:4-3:6-dianhydro-*l*-iditol (1.55 g.); it recrystallised from ethyl acetate as the hemihydrate, m. p. 43–45° alone or in admixture with the starting material.

Attempted Condensation of Dianhydro-*l*-iditol with Benzaldehyde.—The dianhydride (0.55 g.) was shaken with freshly distilled benzaldehyde (10 c.c.) and zinc chloride (0.5 g.) for 48 hours. The resulting suspension was poured into water-ligroin which completely dissolved it. Sodium carbonate (0.5 g.), dissolved in water, was added and the mixture distilled under reduced pressure, with addition of water until all the benzaldehyde was removed. After being evaporated to dryness the residue was extracted with ethyl acetate, and the extract evaporated. From ethyl acetate there crystallised unchanged dianhydro-*l*-iditol hemihydrate (0.4 g.), m. p. 43–45° alone or in admixture with the starting material.

2:5-Bismethanesulphonyl 1:4-3:6-Dianhydro-*l*-iditol.—The dianhydride (0.2 g.), dissolved in dry pyridine (5 c.c.), was treated with methanesulphonyl chloride (0.4 g.) at room temperature. The mixture was kept for 24 hours and then poured into ice-water. The crystalline precipitate was collected; the compound recrystallised from alcohol in long needles, m. p. 155–156°, $[\alpha]_D^{25} + 41.9^\circ$ (c, 1.145 in acetone) (Found: C, 32.2; H, 4.9. $C_8H_{14}O_8S_2$ requires C, 31.8; H, 4.6%).

2:5-Dibenzoyl Dianhydro-*l*-iditol.—The dianhydride (0.1 g.) was dissolved in 5*N*-sodium hydroxide (3 c.c.), and benzoyl chloride (0.3 g. added). After vigorous shaking for $\frac{1}{2}$ hour, the solid which had separated was collected and washed with water; the compound recrystallised from alcohol in plates (0.13 g.), m. p. 110–111°, $[\alpha]_D^{25} + 139.1^\circ$ (c, 1.04 in chloroform) (Found: C, 67.7; H, 4.9. $C_{20}H_{18}O_8$ requires C, 67.8; H, 5.1%).

3:4-Ditosyl Tetra-acetyl Mannitol.—3:4-Ditosyl 1:2-5:6-diacetone mannitol (10 g.) (prepared by the method of Brigl and Gruner, *loc. cit.*) was hydrolysed by heating it for 3 hours at 70° with 70% acetic acid (100 c.c.). The acetic acid was removed under reduced pressure. The resulting syrup was acetylated by boiling with acetic anhydride (26 c.c.) and sodium acetate (10 g.). The mixture was poured into water and the product neutralised with sodium bicarbonate and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. The compound was a syrup (7.5 g.) which could not be induced to crystallise; $[\alpha]_D^{25} - 0.8^\circ$ (c, 10.23 in chloroform) (Found: S, 9.6. $C_{28}H_{44}O_{14}S_2$ requires S, 9.7%).

Treatment of 3:4-Ditosyl Tetra-acetyl Mannitol with Sodium Methoxide.—The syrup (7.5 g.) was dissolved in chloroform (100 c.c.), and sodium methoxide (4 g.), dissolved in dry methyl alcohol (40 c.c.), added at 0°. The mixture was allowed to warm up to room temperature and to remain thereat for 4 hours. The mixture was extracted with water and separated from the chloroform layer. The aqueous extract was neutralised with *N*-sulphuric acid and the solution evaporated to dryness. The residue was extracted with ethyl acetate, and on evaporation of this solvent a syrup (0.9 g.) was obtained. This distilled at 160° (bath temp.)/0.08 mm. and showed $n_D^{20} 1.4925$, $[\alpha]_D^{25} - 16.7^\circ$ (c, 5.27 in water) (Found: C, 48.8; H, 6.8. $C_8H_{10}O_4$ requires C, 49.3; H, 6.8%). The product crystallised but it was not possible to recrystallise it.

2:5-Dibenzoyl 1:4-3:6-Dianhydro-*d*-iditol.—The above distillate (0.8 g.) was dissolved in 5*N*-sodium hydroxide; benzoyl chloride (2 c.c.) was added, and the mixture shaken vigorously for $\frac{1}{2}$ hour. The dibenzoyl derivative was collected, washed with water, and recrystallised from alcohol. Yield, 0.94 g.; m. p. 110–111°; $[\alpha]_D^{25} - 138.6^\circ$ (c, 3.475 in chloroform) (Found: C, 68.0; H, 5.2. $C_{20}H_{18}O_8$ requires C, 67.8; H, 5.1%).

2 : 5-Bismethanesulphonyl 1 : 4-3 : 6-Dianhydro-d-*iditol*.—Dianhydro-*d*-*iditol* (0.3 g.) was dissolved in dry pyridine (6 c.c.) and methanesulphonyl chloride (0.8 g.) added at 0°. The mixture was kept at room temperature for 74 hours and was then poured into ice-water, and the solid which had separated was collected and washed with water; the compound recrystallised from alcohol in the form of needles. Yield, 0.25 g.; m. p. 156°; $[\alpha]_D^{25} - 41.2^\circ$ (c, 1.41 in acetone) (Found: C, 32.1; H, 4.3. $C_8H_{14}O_8S_2$ requires C, 31.8; H, 4.6%).

Fletcher and Goepf (*loc. cit.*) give, for anhydrous dianhydro-*l*-*iditol*, m. p. 63.7—64.5°, $[\alpha]_D + 20.8^\circ$ (in water), and for the dibenzoate, m. p. 111—111.3°, $[\alpha]_D + 141.9^\circ$ (in chloroform).

The author is grateful to Sir Norman Haworth, F.R.S., for his interest in this work, and to the Colonial Products Research Council for financial aid.

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[Received, December 24th, 1946.]

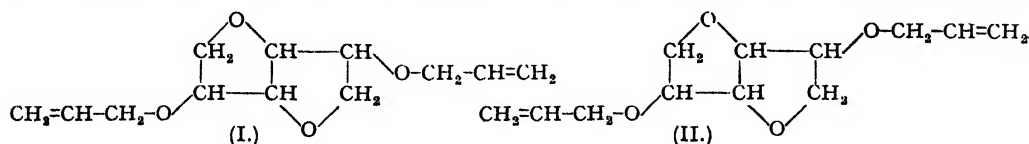
265. Anhydrides of Polyhydric Alcohols. Part VIII. Some Alkenyl Ethers of 1 : 4-3 : 6-Dianhydromannitol and 1 : 4-3 : 6-Dianhydrosorbitol.

By HILDA GREGORY and L. F. WIGGINS.

Diallyl and dimethallyl ethers of the 1 : 4-3 : 6-dianhydrides of mannitol and sorbitol have been prepared. They polymerise slowly in a stream of oxygen, the allyl at a greater rate than the methallyl ethers.

IN continuation of our studies of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol described in Parts I and IV—VII of this series, we have sought to obtain unsaturated ethers of these compounds. In a previous communication (Haworth, Gregory, and Wiggins, *J.*, 1946, 488) we have described unsaturated acyl derivatives of these dianhydrides, namely the diacrylyl and dimethacrylyl esters, which were found to polymerise very rapidly to glass-like resins; saturated ether derivatives have also been reported (Haworth and Wiggins; Patent Application 1945).

The allyl ethers of certain carbohydrates have recently been obtained by Nichols and Yanovsky and their associates; these include allyl sucrose (Nichols and Yanovsky, *J. Amer. Chem. Soc.*, 1945, **67**, 47), tetra-allyl α -methylglucoside (*idem, ibid.*, 1944, **66**, 1625), and allyl starch (Nichols, Hamilton, Smith, and Yanovsky, *Ind. Eng. Chem.*, 1945, **37**, 206). By treating 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol with allyl bromide and concentrated sodium hydroxide solution according to the procedure of Nichols and Yanovsky, we have obtained 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol (I) and 2 : 5-diallyl 1 : 4-3 : 6-dianhydrosorbitol (II), complete allylation being accomplished in one treatment, giving 70% yields of the



products. Both compounds were yellow liquids, quite stable to distillation. Although they polymerised slowly in a stream of oxygen, no appreciable effect was observed on heating them in the presence of benzoyl peroxide, a fact previously noted by Nichols and Yanovsky for tetra-allyl α -methylglucoside. The rates of polymerisation of the dianhydrohexitol derivatives at 97° have been followed viscometrically in an Ostwald viscometer modified as shown in Fig. 1, so that oxygen could be bubbled through the substance and the viscosity measured in the same apparatus.

Preliminary experiments showed that the rate of polymerisation depended upon the rate of flow of oxygen through the apparatus, hence the flow of gas was kept constant throughout the polymerisation. It was found that the rate of polymerisation as measured by the viscosity for both the mannitol and the sorbitol derivatives (see Fig. 2) followed closely the behaviour of tetra-allyl α -methylglucoside, described by Nichols and Yanovsky (*loc. cit.*). Fig. 2 shows that the polymerisation of the mannitol derivative was very slightly faster than that of its sorbitol analogue. Both liquids became darker at the beginning of the heating, but became progressively lighter in colour as the polymerisation continued. The viscosity increased slowly for about 180 minutes, followed by a rapid increase to the gelation point, at which the substances were almost colourless. Both end-products were soft and rubbery, completely infusible and insoluble.

On treatment of dianhydromannitol with methallyl chloride and concentrated sodium hydroxide solution at ordinary pressures, 2 : 5-dimethallyl 1 : 4-3 : 6-dianhydromannitol was obtained in poor yield, owing probably to loss of reagent and incompleteness of reaction. Some improvement was effected by carrying out the reaction in an autoclave fitted with a stirring device, and by this method 2 : 5-dimethallyl-1 : 4-3 : 6-dianhydrosorbitol was obtained. Both of the methallyl derivatives were yellow liquids which polymerised slowly on being heated in a stream of oxygen. Neither, however, gelatinised, or reached a state of acetone insolubility, as distinct from the behaviour of the corresponding allyl derivatives. The rates of polymerisation (see Fig. 2) when investigated under the same conditions as described previously were also markedly slower than those of the allyl ethers; even after 24 hours at 97° in a stream of oxygen at 10 l./hour, no gel formation had occurred and the viscous liquid remained acetone soluble.

FIG. 2.

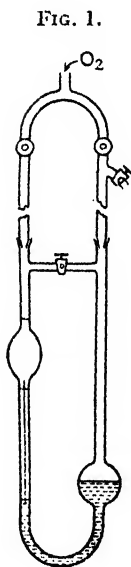
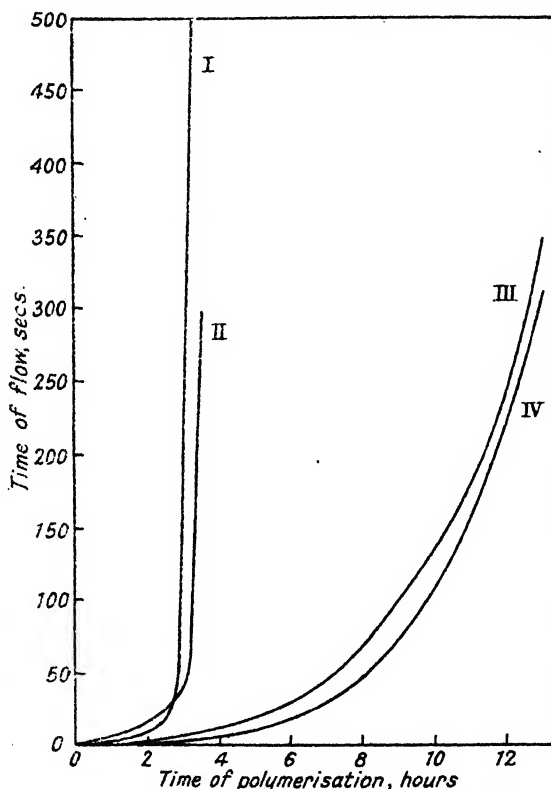


FIG. 1.

- I. 2 : 5-Diallyl 1 : 4-3 : 6-dianhydromannitol.
 II. 2 : 5-Diallyl 1 : 4-3 : 6-dianhydrosorbitol.
 III. 2 : 5-Dimethallyl 1 : 4-3 : 6-dianhydrosorbitol.
 IV. 2 : 5-Dimethallyl 1 : 4-3 : 6-dianhydromannitol.

The difference in the rates of polymerisation of the allyl and methallyl ethers and the difference in properties of the final product must be due to the presence of the methyl group. Therefore, since the methallyl ethers polymerise more slowly and to a lesser degree than the allyl ethers, the methyl group must exhibit an inhibitory effect upon polymerisation. This tendency has been observed previously in many cases. For instance, whereas styrene will undergo addition polymerisation very rapidly, to form long-chain macromolecules, α -methylstyrene will only form an octamer (Staudinger and Breusch, *Ber.*, 1929, 62, 442), and β -methylstyrene, dimeric molecules (Errera, *Gazzetta*, 1884, 14, 504).

EXPERIMENTAL.

2 : 5-Diallyl 1 : 4-3 : 6-Dianhydrosorbitol.—Dianhydrosorbitol (50 g.) was suspended in allyl bromide (85 c.c.) in a three-necked bolthead flask, fitted with a dropping funnel, condenser, and mechanical

stirring device. The well-stirred reaction mixture was maintained at 70°. Sodium hydroxide solution (53 c.c. of a 52% solution, w/v) was added slowly during 1.25 hours, and stirring continued for a further 1.75 hours. Water (100 c.c.) was then added, and any unsaturated volatile compounds present were removed by steam distillation. The mixture was then extracted with ether, the ethereal extract washed with water and dried (MgSO_4), and the ether removed, leaving a light brown, mobile liquid. This was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide. The bulk distilled at 157–161°/20 mm. One further distillation gave pure *diallyl dianhydrosorbitol* as a colourless liquid in 70.3% yield, b. p. 185°/40 mm., n_D^{20} 1.4812, $[\alpha]_D^{20} + 93.4^\circ$ (c, 1.756 in chloroform) (Found: C, 63.4; H, 7.7. $\text{C}_{12}\text{H}_{18}\text{O}_4$ requires C, 63.6; H, 8.0%).

The rate of polymerisation of 2:5-diallyl dianhydrosorbitol was followed viscometrically. The results below give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses): 1.9 (0); 2.4 (20); 2.8 (45); 18 (130); 37.0 (166); 118.0 (196); 160 (205); 245.0 (210); ∞ (216). During the last reading the material gelled in the tube. These results are shown graphically in Fig. 2.

2:5-Diallyl 1:4:3:6-Dianhydromannitol.—This was prepared on the same scale and in the same way as its sorbitol analogue. The compound was obtained as a colourless, mobile liquid, b. p. 173°/10 mm., n_D^{20} 1.4847, $[\alpha]_D^{20} + 160.3^\circ$ (c, 1.51 in chloroform) (Found: C, 63.2; H, 8.3. $\text{C}_{12}\text{H}_{18}\text{O}_4$ requires C, 63.6; H, 8.0%).

The rate of polymerisation of 2:5-diallyl dianhydromannitol was investigated viscometrically. The following results give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses): 1.4 (0); 1.8 (20); 2.4 (80); 5.6 (105); 15.1 (135); 32.4 (155); 82.0 (170); 120.0 (180); 495.2 (185); ∞ (193). These results are shown graphically in Fig. 2.

2:5-Dimethylallyl 1:4:3:6-Dianhydromannitol.—A mixture of 1:4:3:6-dianhydromannitol (20.0 g.), methallyl chloride (100 c.c.), and sodium hydroxide (22 c.c. of a 52% solution, w/v) was heated on a boiling water-bath for 10 hours. The mixture was kept well stirred throughout the reaction to prevent the conversion of methallyl chloride into isobutaldehyde as a result of the development of local acidity. The mixture was then cooled, water (200 c.c.) was added, and the two layers were separated. The upper layer was dried (CaCl_2) and distilled on a boiling water-bath under reduced pressure to remove the more volatile components. The residual oil was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide. The bulk distilled at 132–135°/10 mm. as a pale yellow liquid which darkened on standing. One further distillation under the same conditions gave 2:5-dimethylallyl 1:4:3:6-dianhydromannitol (4.62 g.), b. p. 135°/10 mm., n_D^{20} 1.4979, $[\alpha]_D^{20} + 71.4^\circ$ (c, 1.168 in chloroform) (Found: C, 66.0; H, 8.3. $\text{C}_{14}\text{H}_{22}\text{O}_4$ requires C, 66.1; H, 8.6%). The rate of polymerisation of 2:5-dimethylallyl 1:4:3:6-dianhydromannitol was investigated viscometrically. The following results give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses): 2.5 (0); 3.0 (60); 4.0 (120); 2 (150); 5.8 (195); 8.0 (240); 11.2 (300); 18.0 (360); 27.8 (420); 35.0 (450); 52.2 (480); 1400 (990). Further readings could not be taken owing to the high viscosity of the liquid. These results are shown graphically in Fig. 2.

2:5-Dimethylallyl 1:4:3:6-Dianhydrosorbitol.—Dianhydrosorbitol (20 g.), methallyl chloride (100 g.), sodium hydroxide solution (22 c.c. of a 50% solution, w/v), and acetone (100 c.c.) were heated in a stainless steel autoclave, fitted with a stirring device, for 10 hours at 120°. The contents of the autoclave were then diluted with water (200 c.c.) and the mixture was steam distilled to remove acetone, methallyl chloride, and any methallyl alcohol and dimethylallyl ether produced during the reaction. The remaining liquid was then cooled and extracted with ether, the ethereal extract was washed with water and dried (MgSO_4), and the ether was removed. The residual brown mobile liquid was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide, whereby a pale yellow liquid was obtained, b. p. 150–160°/15 mm. The distillate was then redistilled using the same precautions; dimethylallyl dianhydrosorbitol (6.4 g.) was obtained, b. p. 157°/15 mm., n_D^{20} 1.4843, $[\alpha]_D^{20} + 37.1^\circ$ (c, 1.40 in chloroform) (Found: C, 66.0; H, 8.7. $\text{C}_{14}\text{H}_{22}\text{O}_4$ requires C, 66.1; H, 8.66%).

The rate of polymerisation of 2:5-dimethylallyl dianhydrosorbitol was followed viscometrically. The results below give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses): 1.9 (0); 2.6 (60); 14.4 (255); 20.5 (295); 26.6 (330); 30.0 (360); 36.4 (390); 44.0 (420); 52.0 (440); 64.5 (475); 85.0 (515); 88.6 (540); 123.0 (570); 133.0 (600); 195.0 (675); 315.0 (750); 581.0 (810); 1423 (970). Further readings could not be taken in this apparatus owing to the high viscosity of the liquid. The results are shown graphically in Fig. 2.

The authors wish to express their thanks to Sir Norman Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest, and to the Colonial Products Research Council for financial assistance.

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[Received, December 24th, 1946.]

266. The Preparation of 1:8-Naphthyridines from 2:6-Diaminopyridine.

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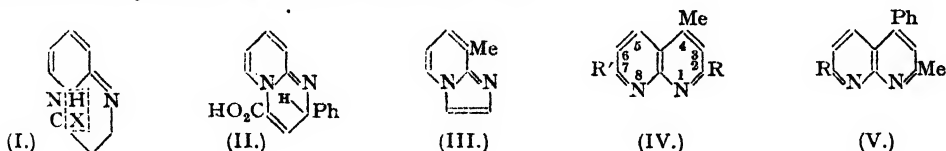
7-Amino-2-hydroxy-4-methyl-1:8-naphthyridine (IV; $\text{R} = \text{OH}$, $\text{R}' = \text{NH}_2$), prepared by condensation of ethyl acetoacetate or ethyl β -aminocrotonate with 2:6-diaminopyridine, has been converted into 2-chloro-7-acetamido-4-methyl-1:8-naphthyridine (IV; $\text{R} = \text{Cl}$, $\text{R}' = \text{NHAc}$), and hence into 2-anilino-, 2-p-chloroanilino-, 2-piperidino-, and 2-phenoxy-7-amino-4-methyl-1:8-naphthyridine.

Condensation of benzoylacetone with 2:6-diaminopyridine gives 7-amino-4-phenyl-2-methyl-1:8-naphthyridine (V; R = NH₂), converted into 7-hydroxy-, 7-chloro-, and hence into 7-anilino-, 7-piperidino-, and 7-phenoxy-4-phenyl-2-methyl-1:8-naphthyridine. (V; R = NHAc) gives the 1(N)-monoquaternary salt.

Our interest in the naphthyridines arose from the chance observation that certain members of the series possessed valuable biological properties (see Petrow, *J.*, 1946, 200), and a comprehensive survey of the field is now in progress in these Laboratories. The present communication describes some new derivatives of 1:8-naphthyridine. Biological data will be reported elsewhere.

Although 2-aminopyridine would appear to form the obvious starting point for the synthesis of 1:8-naphthyridines, they have not hitherto been prepared from this base. Earlier claims to this effect by Reissert (*Ber.*, 1895, 28, 119) and R  th (*Annalen*, 1931, 486, 284; see also E.P.P. 319,974, 339,932 and G.P.P. 526,630, 522,272) have been conclusively disproved by Bose and Sen (*J.*, 1931, 2840), Seide and Chelinzwen (*J. Gen. Chem. Russia*, 1937, 7, 2314), Sp  th and Kuffner (*Ber.*, 1938, 71, 1657), and Petrow (*J.*, 1945, 928). It would appear that 2-aminopyridine reacts preferentially in the imino-form [partial formula (I)] to give the pyrimidine ring system such as (II) in cases of ring closure. Reactions with ethyl acetoacetate (Crippa and Scevola, *Gazzetta*, 1937, 67, 330), ethyl benzoylacetate (Seide, *Ber.*, 1925, 58, 352; cf. Palazzo and Tamburini, *Atti R. Accad. Lincei*, 1911, 20, I, 37), ethyl malonate (Tschitschibabin, *Ber.*, 1924, 57, 1169), and ethylene oxide (Kunzjanz, *Ber.*, 1935, 68, 397) have been shown to fall into this category. The recent claim of Mazza and Migliardi (*Atti R. Accad. Sci. Torino*, 1940, 75, I, 438; see also Migliardi, *ibid.*, p. 548) that reaction of 2-aminopyridine with benzaldehyde and pyruvic acid leads to a 4-carboxy-2-phenyl-1:8-naphthyridine cannot be accepted. There seems little doubt that their product should be correctly formulated as the pyrimidine derivative (II). R  th (*Ber.*, 1925, 58, 347; cf. Tschitschibabin, *ibid.*, p. 1704) has described the formation of a "1:2-dihydro-1:8-naphthyridine" in low yield from the products of reaction of 2-amino-3-methylpyridine with bromoacetal at 250  . This claim, too, must be accepted with caution, as it seems unreasonable to assume the stability of a 1:2-dihydro-structure under the conditions of the experiment. In our view, this reaction leads to the 8-methylpyrimidazole (III). The facile formation of ring systems of this type has been demonstrated by Schmidt and Bangler (*Ber.*, 1926, 59, 1360), Tschitschibabin (*loc. cit.*), and Allen *et al.* (*J. Amer. Chem. Soc.*, 1944, 66, 1805). 2-Aminopyridine behaves as a cyclic amidine in these reactions, and on electro-chemical grounds alone its conversion into a 1:8-naphthyridine appears highly improbable.

2:6-Diaminopyridine, in striking contrast to 2-aminopyridine, forms the most accessible starting material for the synthesis of 1:8-naphthyridines, owing probably to the presence of two amino-groupings in the molecule either of which can take part in the prototropic change involved in imine-formation. By direct condensation of the base with ethyl acetoacetate, Seide (*Ber.*, 1926, 59, 2465) obtained 7-amino-2-hydroxy-4-methyl-1:8-naphthyridine (IV; R = OH, R' = NH₂) in good yield. The reaction has been extended to ethyl benzoylacetate (Mangini and Colonna, *Gazzetta*, 1942, 72, 183), acetylacetone (Mangini, *Chem. Zentr.*, 1940, II, 2613; Ochiai and Miyaki, *Ber.*, 1941, 74, 1115), and ethoxymethylene diethylmalonate (Adams *et al.*, *J. Amer. Chem. Soc.*, 1946, 68, 1317).



We now find that 7-amino-2-hydroxy-4-methyl-1:8-naphthyridine (IV; R = OH, R' = NH₂) (Seide, *loc. cit.*) passes smoothly under the action of acetic anhydride into 7-acetamido-2-hydroxy-4-methyl-1:8-naphthyridine (Mangini and Colonna, *loc. cit.*). The acetamidogrouping in this compound proved stable to phosphorus oxychloride, giving 2-chloro-7-acetamido-4-methyl-1:8-naphthyridine (IV; R = Cl, R' = NHAc), occasionally mixed with some 2-chloro-7-amino-4-methyl-1:8-naphthyridine. Treatment of (IV; R = Cl, R' = NHAc) with phenol at 180   gave 7-acetamido-2-phenoxy-4-methyl-1:8-naphthyridine, hydrolysed to the corresponding amino-derivative. 7-Amino-2-anilino-, 7-amino-2-p-chloroanilino-, and 7-amino-2-piperidino-4-methyl-1:8-naphthyridine were similarly prepared.

Condensation of 2:6-diaminopyridine with benzoylacetone in the presence of zinc chloride

gave 7-amino-4-phenyl-2-methyl-1 : 8-naphthyridine (V; R = NH₂), characterised by preparation of the *picrate*. The derived acetamido-compound (V; R = NHAc) was converted *via* the methosulphate into 7-acetamido-4-phenyl-2-methyl-1 : 8-naphthyridine-1-methiodide, and hence into the corresponding methochloride. The constitution assigned to the monomethiodide followed from the formation of a highly coloured dye on heating the compound with *p*-dimethylaminobenzaldehyde in alcoholic solution containing a trace of piperidine. This colour change is almost certainly due to the formation of the corresponding 2-*p*-dimethylamino-styryl derivative, but attempts to isolate it in a state of analytical purity were unsuccessful. Treatment of (V; R = NH₂) with nitrous acid gave 7-hydroxy-4-phenyl-2-methyl-1 : 8-naphthyridine (V; R = OH), from which 7-chloro-, and hence 7-phenoxy-, 7-anilino-, and 7-piperidino-4-phenyl-2-methyl-1 : 8-naphthyridine were readily prepared. Attempts to condense (V; R = NH₂) with *p*-acetamidobenzenesulphonyl chloride were unsuccessful.

We have *inter alia* examined the condensation of ethyl β -aminocrotonate with 2 : 6-diaminopyridine in the hope of obtaining the isomeric 7-amino-4-hydroxy-2-methyl-1 : 8-naphthyridine, but the only product isolated as (IV; R = OH, R' = NH₂) in somewhat better yield. The corresponding nitrile, β -aminocrotononitrile, it may be added, reacts with arylamines with exceptional facility to give the β -aryliminobutyronitriles by loss of the elements of ammonia (Meyer, *J. pr. Chem.*, 1908, 78, 499). Its behaviour with the aminopyridines will form the subject of a later communication.

EXPERIMENTAL.

(M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (IV; R = Cl, R' = NHAc).—7-Acetamido-2-hydroxy-4-methyl-1 : 8-naphthyridine was prepared by heating finely powdered (IV; R = OH, R' = NH₂) (Seide, *Ber.*, 1926, 59, 2465) (2 g.) with acetic anhydride (30 ml.) under reflux for 30 mins. The heavy yellow solid changed to a flocculent white suspension. When cold, the product was collected and recrystallised from a large volume of glacial acetic acid (charcoal), giving white crystals, m. p. >310° (Found: C, 60.8; H, 5.2; N, 19.0. Calc. for C₁₁H₁₁O₂N₃ C, 60.8; H, 5.1; N, 19.3%). Yield 2.2 g. (89%) (Mangini and Colonna, *loc. cit.*, give m. p. <285°). The acetamido-compound (10 g.) was heated with phosphorus oxychloride (100 ml.) for 30 minutes under reflux. The product was decomposed with ice-water and made alkaline with sodium hydroxide, and the precipitated solids were recrystallised from spirit. 2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine formed felted white needles (7.5 g.; 69%), m. p. 240° (Found: C, 55.9; H, 3.8; N, 17.8; Cl, 15.6. C₁₁H₁₀ON₂Cl requires C, 56.1; H, 4.2; N, 17.8; Cl, 15.1%).

If the temperature rose somewhat during the decomposition of the phosphorus oxychloride reaction mixture, 2-chloro-7-amino-4-methyl-1 : 8-naphthyridine, white needles, m. p. 258–259°, from alcohol (Found: Cl, 21.3. C₉H₇N₃Cl requires Cl, 21.7%), was also obtained, readily separated from the acetamido-compound by fractionation from alcohol in which it was less soluble. On acetylation it gave the acetamido-derivative, m. p. 240° (above).

7-Acetamido-2-phenoxy-4-methyl-1 : 8-naphthyridine.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (1 g.) was heated with phenol (3 g.) at 180° for 1 hour. The cooled melt was treated with excess of sodium hydroxide solution, and the insoluble fraction collected and heated with acetic anhydride on the water-bath. 7-Acetamido-2-phenoxy-4-methyl-1 : 8-naphthyridine, separated on cooling as long needles from aqueous alcohol, m. p. 205° (Found: C, 69.3; H, 5.2; N, 14.1. C₁₇H₁₅O₂N₃ requires C, 69.6; H, 5.1; N, 14.3%). Hydrolysis with alcoholic hydrochloric acid gave 7-amino-2-phenoxy-4-methyl-1 : 8-naphthyridine, needles from benzene, m. p. 216–217° (Found: C, 71.6; H, 5.3; N, 16.7. C₁₅H₁₃ON₃ requires C, 71.8; H, 5.2; N, 16.7%).

7-Amino-2-anilino-4-methyl-1 : 8-naphthyridine (IV; R = NHPh, R' = NH₂).—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (4 g.) was heated with aniline (10 ml.) under reflux for 3 hours. Excess of aniline was removed in steam, and the solids were collected and heated under reflux with 2*N*-hydrochloric acid for 1 hour. The mixture was made alkaline with sodium hydroxide and the product purified from spirit. 7-Amino-2-anilino-4-methyl-1 : 8-naphthyridine formed yellow crystals, m. p. 269–270° (Found: C, 71.6; H, 5.4; N, 23.0. C₁₅H₁₄N₄ requires C, 72.0; H, 5.6; N, 22.4%).

7-Amino-2-*p*-chloroanilino-4-methyl-1 : 8-naphthyridine.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (2.5 g.) and *p*-chloroaniline (2.5 g.) were heated under reflux in nitrobenzene (25 ml.). Vigorous reaction occurred in a few minutes and the mixture set to a semi-solid. Heating at 200° was continued for one hour. The yellow-brown solids were collected and crystallised from alcohol-light petroleum. 7-Amino-2-*p*-chloroanilino-4-methyl-1 : 8-naphthyridine formed ivory needles (1 g.; 33%), m. p. 224–225° (Found: C, 63.1; H, 4.9; N, 19.5; Cl, 12.5. C₁₄H₁₃N₄Cl requires C, 63.3; H, 4.6; N, 19.7; Cl, 12.5%). The hydrochloride formed yellow needles from alcohol-light petroleum, m. p. >300° (Found: Cl, 22.8. C₁₄H₁₃N₄Cl₂ requires Cl, 22.9%).

7-Amino-2-piperidino-4-methyl-1 : 8-naphthyridine.—(IV; R = Cl, R' = NHAc) (1 g.) was heated with piperidine (5 ml.) at 180° for 8 hours in a sealed tube. Excess of piperidine was removed on the water-bath. The crystalline product, after hydrolysis with concentrated hydrochloric acid (10 ml.) and alcohol (25 ml.) for 1 hour, followed by basification with sodium hydroxide, gave 7-amino-2-piperidino-4-methyl-1 : 8-naphthyridine, ivory crystals from light petroleum, m. p. 221.5–222.5° (Found: C, 69.0; H, 7.2; N, 22.7. C₁₄H₁₅N₄ requires C, 69.4; H, 7.4; N, 23.1%).

7-Amino-4-phenyl-2-methyl-1 : 8-naphthyridine (V; R = NH₂).—2 : 6-Diaminopyridine (20 g.), benzoylacetone (30 g.), and powdered anhydrous zinc chloride (12 g.) were heated in an oil-bath. Reaction

commenced at 135°, after which the temperature was slowly raised to 175° over 3½ hours. Solution in alcohol (200 ml.) followed by gradual precipitation with water (300 ml.) gave a granular product, further purified by solution in 2*N*-hydrochloric acid (charcoal) and precipitation with sodium hydroxide. For purification, the crude naphthylidine (8 g.) and acetic anhydride (80 ml.) were heated under reflux for 30 minutes. 7-Acetyl-4-phenyl-2-methyl-1:8-naphthylidine, needles from benzene (30%), m. p. 207–208° (Found: C, 73.4; H, 5.4; N, 15.0. $C_{17}H_{15}ON_2$ requires C, 73.6; H, 5.4; N, 15.2%), separated on cooling. Hydrolysis with boiling 15% hydrochloric acid for 30 minutes gave 7-amino-4-phenyl-2-methyl-1:8-naphthylidine, pale yellow octahedra from nitrobenzene, m. p. 247.5–248.5° (Found: C, 76.4; H, 5.6; N, 18.1. $C_{18}H_{17}N_3$ requires C, 76.6; H, 5.5; N, 17.9%), characterised as the *picrate*, fine yellow needles from a large volume of alcohol, m. p. 284° (decomp.) (Found: N, 18.1. $C_{18}H_{13}N_3 \cdot C_6H_3O_7N_3$ requires N, 18.1%).

7-Acetyl-4-phenyl-2-methyl-1:8-naphthylidine-1-(*N*)-methiodide, prepared via the methosulphate, formed silky yellow needles (75%) from alcohol, m. p. 244–245° (Found: I, 31.2. $C_{18}H_{15}ON_2I$ requires I, 30.4%). The methochloride formed pale green platelets from alcohol-ether, m. p. 235–236° (Found: Cl, 11.1. $C_{18}H_{15}ON_2Cl$ requires Cl, 10.8%).

7-Hydroxy-4-phenyl-2-methyl-1:8-naphthylidine (V; R = OH).—The amino-compound (V; R = NH_2) (10 g.) in water (250 ml.) and concentrated hydrochloric acid (5 ml.), mechanically stirred at 0°, was treated simultaneously during 30 minutes with sodium nitrite (4.5 g. in 20 ml. water) and hydrochloric acid (10 ml. in 30 ml. water). After 2 hours the mixture was heated on the water-bath until evolution of nitrogen had ceased. The product was precipitated with ammonium hydroxide (d 0.88), giving 7-hydroxy-4-phenyl-2-methyl-1:8-naphthylidine, needles from alcohol, m. p. 252–253° (Found: C, 76.3; H, 5.2; N, 11.6. $C_{18}H_{17}ON_2$ requires C, 76.2; H, 5.1; N, 11.9%). The compound dissolves in sodium hydroxide solution.

7-Chloro-4-phenyl-2-methyl-1:8-naphthylidine (V; R = Cl).—The hydroxy-compound (V; R = OH) (2 g.) and phosphorus oxychloride (15 ml.) were heated under reflux at 140–150° for 30 minutes. The product, isolated in the usual way, gave 7-chloro-4-phenyl-2-methyl-1:8-naphthylidine (70%), felted needles from aqueous methanol (charcoal), m. p. 161° (Found: Cl, 14.4. $C_{18}H_{15}N_2Cl$ requires Cl, 14.0%).

7-Phenoxy-4-phenyl-2-methyl-1:8-naphthylidine separated from benzene–light petroleum in needles (80%), m. p. 156–157.5° (Found: C, 80.6; H, 5.3; N, 8.9. $C_{21}H_{19}ON_2$ requires C, 80.7; H, 5.2; N, 8.9%).

7-Anilino-4-phenyl-2-methyl-1:8-naphthylidine formed pale yellow needles from a large volume of alcohol, m. p. 286–287° (Found: C, 80.4; H, 5.6; N, 13.3. $C_{21}H_{17}N_3$ requires C, 81.0; H, 5.5; N, 13.5%).

7-Piperidino-4-phenyl-2-methyl-1:8-naphthylidine, isolated as the *picrate*, long yellow needles from alcohol, m. p. 220–221° (decomp. at 238°) (Found: N, 15.7. $C_{20}H_{21}N_3 \cdot C_6H_3O_7N_3$ requires N, 15.8%), formed pale yellow plates from benzene–light petroleum, m. p. 131–132° (Found: C, 79.0; H, 7.0; N, 14.0. $C_{20}H_{21}N_3$ requires C, 79.2; H, 6.9; N, 13.9%).

7-Amino-2-hydroxy-4-methyl-1:8-naphthylidine (IV; R = OH, R' = NH_2).—2:6-Diaminopyridine (5 g.) and ethyl β-aminocrotonate (6 g.) were heated at 180–200° for 2 hours, after which the temperature was raised to 220° during 45 minutes, the mixture then solidifying. The grey-green mass was extracted with alcohol, giving (IV; R = OH, R' = NH_2), m. p. >360°, identified by acetylation and chlorination to (IV; R = Cl, R' = $NHAc$), m. p. 240°, alone or in admixture with an authentic specimen (above), further converted into (IV; R = *OPh*, R' = NH_2), m. p. 214–215°, alone or in admixture with an authentic specimen.

The authors thank the Therapeutic Research Corporation of Great Britain Limited for grants and for certain facilities.

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[Received, December 31st, 1946.]

267. Contributions to the Chemistry of Phenanthridine. Part I. The Conversion of 9-(3'-Pyridyl)phenanthridines into their Quaternary Salts and the Preparation of Some Derivatives of Potential Biological Interest.

By V. PETROW and W. R. WRAGG.

9-(3'-Pyridyl)- (II; R = R' = H), 3-nitro-9-(3'-pyridyl)- (II; R = NO_2 , R' = H), and 7-nitro-9-(3'-pyridyl)-phenanthridine (II; R = H, R' = NO_2) have been obtained from the appropriate 2-nicotinamidodiphenyls. Conversion of the first two compounds into their mono-quaternary salts led to the formation of the py-N-methylmethosulphates, the constitution of which followed from their oxidation to the corresponding N-methylpyridones.* As expected, the monomethiodide derived from 9-(6'-keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine (IV; R = H) possessed the anticipated properties of a phenanthridyl-N-methiodide.

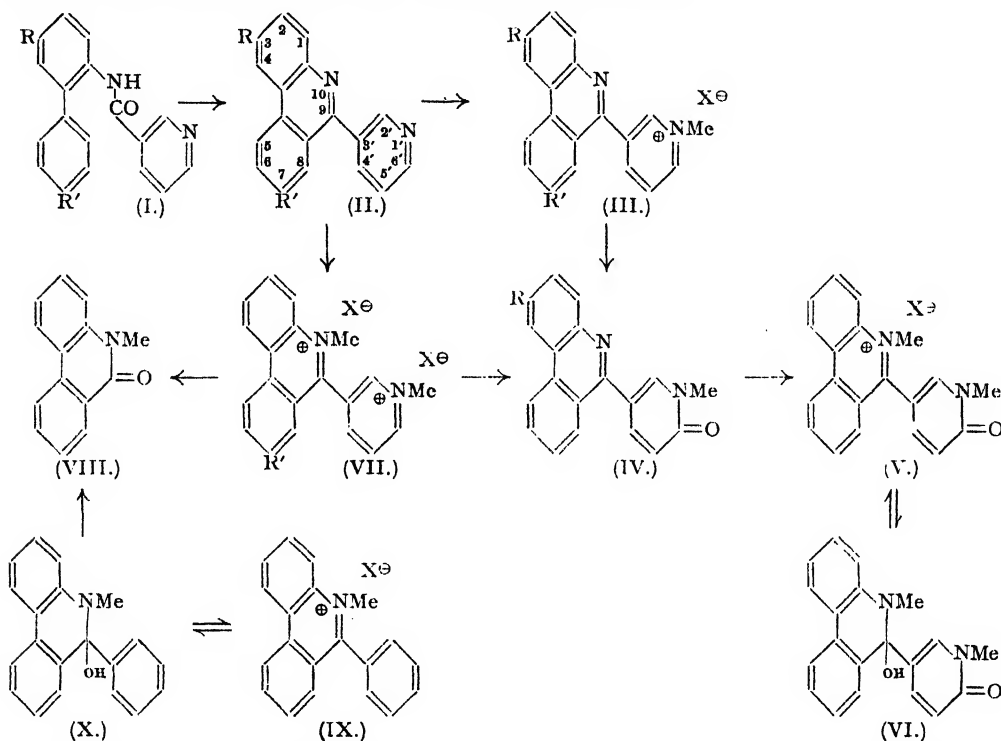
Treatment of 9-(3'-pyridyl)phenanthridine 1':10-dimethiodide (VII; R' = H, X = I) with excess of aqueous sodium hydroxide followed by potassium ferricyanide at room temperature gave (IV; R = H). Reaction with boiling alcoholic sodium hydroxide, however, resulted in

* These N-methylpyridones may clearly be either 2'- or 6'-pyridones. The question is irrelevant to the present investigation and the orientation of a 6'-pyridone has been assumed throughout.

loss of the pyridyl-1'-methiodide grouping and the production of 10-methyl-9-phenanthridone (VIII), also obtained by the action of alcoholic alkaline ferricyanide on 9-phenylphenanthridine 10-methylmethosulphate (IX; X = MeSO₃).

Reduction of the two nitro-9-(3'-pyridyl)phenanthridines (II; R = NO₂, R' = H, and R = H, R' = NO₂) and their py-N-methylmethosulphates gave the corresponding amino-compounds.

FOLLOWING recent work on the relationship between structure and biological activity in the phenanthridine series (Petrov, *J.*, 1945, 18; Walls, *ibid.*, p. 294), we have now synthesised some 9-(3'-pyridyl)phenanthridines. We required these for examination as trypanocides, and also, from their formal analogy to the pyridyl quinolines of Coates, Cook, Heilbron, Hey, Lambert, and Lewis (*J.*, 1943, 401), for study as spasmolytics.



Condensation of nicotinyl chloride hydrochloride with 2-aminodiphenyl in boiling chlorobenzene solution led to the formation of 2-nicotinamidodiphenyl (I; R = R' = H) in 78% yield. 5-Nitro- (I; R = NO₂, R' = H), and 4'-nitro-2-nicotinamidodiphenyl (I; R = H, R' = NO₂) were similarly prepared from the appropriate diphenyls. Ring closure of these compounds failed to take place on heating them with phosphorus oxychloride alone, but was readily accomplished by using phosphorus oxychloride in nitrobenzene solution (B.P. 520, 273; cf. Walls, *loc. cit.*) giving 9-(3'-pyridyl)- (II; R = R' = H) and 3-nitro-9-(3'-pyridyl)-phenanthridine (II; R = NO₂, R' = H) in excellent yields. When 4'-nitro-2-nicotinamidodiphenyl (I; R = H, R' = NO₂) was employed, however, ring closure appeared incomplete after 24 hours' heating, and the yield of 7-nitro-9-(3'-pyridyl)phenanthridine (II; R = H, R' = NO₂) was only 37%. This result is a further illustration of the polar influence of the 4'-nitro-grouping in depressing the mobility of the 2'-hydrogen atom involved in ring closure (cf. Morgan and Walls, *J.*, 1938, 390; Petrov, *loc. cit.*).

Conversion of (II; R = R' = H) into the mono-quaternary salt may clearly involve either the pyridyl or phenanthridyl basic centres. We have decided in favour of the former alternative on the following evidence. Reaction of 9-phenylphenanthridine, a compound structurally related to (II; R = R' = H) but possessing only the phenanthridyl basic centre, with methyl sulphate, led to the formation of 9-phenylphenanthridine 10-methylmethosulphate (IX; X = MeSO₃), converted by one molar equivalent of sodium hydroxide into the pseudo-base (X). Although this reaction may also yield the methohydroxide, it has been assumed by earlier

workers that the product obtained is actually the pseudo-base where experimental evidence favours such a conclusion; pseudo-bases differ from the corresponding quaternary hydroxides in that they are relatively insoluble in water and soluble in non-hydroxylic solvents (*e.g.*, light petroleum). The pseudo-base reverted on treatment with 1.15 molar equivalents of hydrochloric acid to the quaternary salt, converted by potassium iodide into the normal *methiodide*. These model transformations serve to characterise systems such as (IX). The reactions of the monoquaternary salts obtained from (II) with, in the first place, alkali, and secondly potassium ferricyanide-sodium hydroxide, however, followed a different pattern which could be interpreted only by assuming that it was the pyridyl nitrogen which was involved in salt formation. Thus both 9-(3'-pyridyl)phenanthridine 1'-methiodide (III; R = R' = H, X = I) and 3-nitro-9-(3'-pyridyl)phenanthridine 1'-methylmethosulphate (III; R = NO₂, R' = H, X = MeSO₄) failed to give sparingly soluble pseudo-bases when treated with one molar proportion of aqueous sodium hydroxide. (III; R = R' = H; X = I) was unchanged by heating with excess dilute sodium hydroxide for one minute. Treatment of a warm aqueous solution of (III; R = NO₂, R' = H, X = MeSO₄) with a large excess of sodium hydroxide precipitated a red amorphous material, probably the pseudo-base, which on vacuum sublimation gave a very small yield of 3-nitro-9-(6'-keto-1'-methyl-1': 6'-dihydro-3'-pyridyl)phenanthridine (IV; R = NO₂), also obtained in good yield from (III; R = NO₂, R' = H, X = MeSO₄) by hot alkaline ferricyanide oxidation, and characterised as its *hydrochloride*. Attempts to oxidise 9-(3'-pyridyl)phenanthridine 1'-methiodide (III; R = R' = H, X = I) with potassium ferricyanide-sodium hydroxide at room temperature led to the separation of the very sparingly soluble *ferricyanide*. When the reaction was carried out at 80° (cf. Diesbach and Aeschbach, *Helv. Chim. Acta*, 1945, **28**, 1392) in the presence of benzene, oxidation occurred to give 9-(6'-keto-1'-methyl-1': 6'-dihydro-3'-pyridyl)phenanthridine (IV; R = H), characterised by conversion into the *hydrochloride* and the *thiopyridone* derivative.

Conversion of (IV; R = H) into the quaternary salt led to the formation of 9-(6'-keto-1'-methyl-1': 6'-dihydro-3'-pyridyl)phenanthridine 10-methiodide (V; X = I), a compound which now exhibited the typical reactions of the 9-phenyl-10-methylphenanthridinium system (IX). Thus with 1.05 molar equivalent of sodium hydroxide it passed into the *pseudo-base* (VI), converted by 1.1 molar equivalent of hydrochloric acid into the methochloride, which was transformed into the methiodide (V; X = I) with potassium iodide. Attempts to oxidise (V; X = I) with aqueous alkaline ferricyanide at 80° in the presence of benzene were unsuccessful, only the pseudo-base (VI) being isolated.

The conversion of 9-(3'-pyridyl)phenanthridine 1': 10-dimethiodide (VII; R' = H, X = I) into (VI) would complete the series of reactions (II) to (VI) by two separate routes and supply further experimental evidence confirming these formulations. On treatment of (VII; R' = H, X = I) with 50% alcoholic alkaline ferricyanide, however, 10-methyl-9-phenanthridone (VIII) was obtained in place of the expected (VI), the quaternary pyridyl group having been removed. The same product was also formed by employing 9-phenylphenanthridine-10-methylmethosulphate (IX; X = MeSO₄) in place of (VII; R' = H, X = I). Attempts to oxidise (V; X = I) with 50% alcoholic alkaline ferricyanide, however, gave (VI) and not the phenanthridone (VIII). Further work showed that (VII; R' = H, X = I) could be converted into (VIII) by simply refluxing it with 50% alcoholic dilute sodium hydroxide. Treatment of (VII; R' = H, X = I) dissolved in a large excess of cold 2N-sodium hydroxide with potassium ferricyanide in very dilute solution, resulted in the loss of the quaternary group attached to the phenanthridyl nitrogen, the product isolated being (IV; R = H). Pictet and Patry (*Ber.*, 1893, **26**, 1966) have described the alkaline ferricyanide oxidation of phenanthridine 10-methiodide to 10-methyl-9-phenanthridone (VIII), and have also shown (*Ber.*, 1902, **35**, 2534) that steam distillation of phenanthridine 10-methoxyhydroxide yields 10-methyl-9:10-dihydrophenanthridine and (VIII). Morgan and Walls (*J.*, 1938, 391) have obtained (VIII) by heating 9-dimethylaminophenanthridine 10-methiodide with water. The formation of (VIII) from (VII; R' = H; X = I) and (IX; X = I) represents an extension of these observations, in that the elimination of a 9-aryl substituent is involved. This may take place by an oxidation of the tertiary C₉ alcohol (*e.g.*, X), or in the case of (VII; R' = H; X = I) which yields (VIII) by simple treatment with alkali, by direct transference of hydrogen from the C₉ hydroxyl group to the quaternary pyridyl group.

3- (III; R = NH₂, R' = H, X = Cl) and 7-Amino-9-(3'-pyridyl)phenanthridine 1'-methochloride (III; R = H, R' = NH₂, X = Cl) were best prepared from the corresponding *methiodides*. These were obtained by reducing the appropriate nitro-9-(3'-pyridyl)phenanthridine 1'-monomethylmethosulphate with reduced iron in acidified aqueous solution followed

by treatment of the reduction liquor with potassium iodide. Catalytic methods led to nuclear reduction.

3- (II; $R = NH_2$, $R' = H$) and 7-Amino-9-(3'-pyridyl)phenanthridine (II; $R = H$, $R' = NH_2$), obtained from the corresponding nitro-compounds by reduction with stannous chloride, were characterised by preparation of the acetyl derivatives. These gelatinous compounds were obtained crystalline only after sublimation in a high vacuum. 7-Amino-9-(3'-pyridyl)phenanthridine (II; $R = H$, $R' = NH_2$) was also obtained in 31% yield by catalytic reduction of the corresponding nitro-compound in glacial acetic acid with Adams's platinum oxide catalyst. When 2N-hydrochloric acid was substituted as solvent, however, simultaneous nuclear reduction invariably took place. As expected, attempts at the further reduction of the 7-amino-compound (II; $R = H$, $R' = NH_2$) in methanol or glacial acetic acid were unsuccessful, whereas nuclear reduction again occurred in 2N-hydrochloric acid.

The spasmolytic activities of (II; $R = R' = H$), (II; $R = NH_2$, $R' = H$), and (II; $R = H$, $R' = NH_2$) have been very kindly determined for us by Mr. R. Thorp (Wellcome Physiological Research Laboratories, Beckenham, Kent). The L.D.₅₀ of all three compounds, determined by intravenous injection in mice, was approximately 0.06 mg./g. Upon the isolated rabbit intestinal segment, a dilution of 1 : 100,000 of all three substances was about as effective as 1 : 50,000,000 of "trasentin" in relaxing the spasm caused by a 1 : 3,000,000 dilution of carbinoyl choline. Their spasmolytic activity was thus not of a high order.

The results of trypanocidal tests on (III; $R = NH_2$, $R' = H$, $X = Cl$) and (III; $R = H$, $R' = NH_2$, $X = Cl$) have already been reported (Wien, *Brit. J. Pharmacol.*, 1946, 1, 65). At the time these were carried out we had not reached a decision as to the structure of the mono-quaternary salts, to which Dr. Wien provisionally ascribed the phenanthridyl *N*-methochloride formulation.

EXPERIMENTAL.

Semimicro-analyses are by Mr. S. Bance, B.Sc., A.R.I.C., Research Laboratories, May and Baker, Ltd. Melting points are corrected.

2-Nicotinamidodiphenyl (I; $R = R' = H$).—Nicotinic acid (90 g.) was heated under reflux for 1 hour with thionyl chloride (250 c.c.), the mixture taken to dryness under reduced pressure on the water-bath, and the residue dissolved during 20 minutes in boiling chlorobenzene (1 l.). On addition of 2-aminodiphenyl (120 g.) in warm chlorobenzene (200 c.c.) a vigorous reaction occurred with evolution of hydrogen chloride and separation of a red oil which solidified. The solid product was collected, washed with ether, and crystallised from solution in methanol (1 l.) by addition of excess of aqueous ammonia. 2-Nicotinamidodiphenyl formed colourless octahedra from aqueous methanol (157 g.; 78%); m. p. 173—174° (Found: C, 78.8; H, 5.1; N, 10.4. $C_{18}H_{14}ON_2$ requires C, 78.8; H, 5.1; N, 10.2%).

5-Nitro-2-nicotinamidodiphenyl (I; $R = NO_2$, $R' = H$).—Nicotiny chloride hydrochloride (from 5 g. acid) dissolved in boiling chlorobenzene (35 c.c.), was treated with 5-nitro-2-aminodiphenyl (7 g.) for 5 minutes under reflux. After addition of pyridine (10 c.c.) and heating for 5 minutes, the mixture was cooled and the product precipitated with light petroleum (50 c.c.). The free base was obtained by crystallisation from alcohol (150 c.c.)—2N-ammonia (excess). 5-Nitro-2-nicotinamidodiphenyl formed long cream prisms from aqueous alcohol (8.6 g.; 83%); m. p. 160—161° (Found: C, 67.9; H, 4.2; N, 13.3. $C_{18}H_{13}O_2N_3$ requires C, 67.7; H, 4.0; N, 13.2%).

4'-Nitro-2-nicotinamidodiphenyl (I; $R = H$, $R' = NO_2$).—Nicotiny chloride hydrochloride (from 25 g. acid) in boiling chlorobenzene (200 c.c.) was treated with 4'-nitro-2-aminodiphenyl (35 g.) for 30 minutes under reflux. After addition of pyridine (30 c.c.) and a further 15 minutes heating, the product was precipitated with an equal volume of light petroleum (b. p. 100—120°). By solution in pyridine (400 c.c.; charcoal) and precipitation with excess of 2N-ammonia, 4'-nitro-2-nicotinamidodiphenyl was obtained, separating from pyridine—light petroleum (1 : 1) in small cream irregular prisms (40 g.; 77%); m. p. 226—227° (Found: C, 67.7; H, 4.0; N, 13.4. $C_{18}H_{13}O_2N_3$ requires C, 67.7; H, 4.0; N, 13.2%). Attempted preparations of this compound in pyridine at 100° instead of in boiling chlorobenzene yielded a product which could not readily be purified.

9-(3'-Pyridyl)phenanthridine (II; $R = R' = H$).—Phosphorus oxychloride (30 c.c.), 2-nicotinamidodiphenyl (20 g.), and nitrobenzene (200 c.c.) were heated under reflux for 20 hours. The mixture was basified with concentrated ammonia at 0° and the nitrobenzene removed in steam. The solids were collected and dissolved in concentrated hydrochloric acid (200 c.c.; charcoal), and the base was precipitated with ammonia at 0°. 9-(3'-Pyridyl)phenanthridine formed colourless needles from light petroleum (b. p. 80—100°) (13.5 g.; 72%); m. p. 125—127° (Found: C, 84.0; H, 4.7; N, 11.2. $C_{18}H_{13}N_3$ requires C, 84.4; H, 4.7; N, 10.9%). With methyl sulphate (0.95 mol.) in boiling benzene for $\frac{1}{2}$ hour it gave the 1'-methylmethosulphate, converted in aqueous solution into the 1'-methiodide (III; $R = R' = H$, $X = I$), yellow elongated plates from methanol of indefinite m. p. 259—269° (Found: N, 7.2; I, 32.0. $C_{18}H_{12}N_3CH_2I$ requires N, 7.0; I, 32.0%). The 1'-methoferricyanide, obtained by treating a warm aqueous solution of the 1'-methylmethosulphate with potassium ferricyanide, crystallised from aqueous methanol in irregular yellow plates, decomposing above 180° (Found: N, 16.2; Fe, 5.4. $(C_{18}H_{12}N_3)_3Fe(CN)_6$ requires N, 16.4; Fe, 5.4%). Reaction of (II; $R = R' = H$; 5.1 g.) with methyl sulphate (7.6 c.c.; 4 mols.) in dry nitrobenzene (400 c.c.) at 170—180° for 30 minutes gave the 1' : 10-dimethyldimethosulphate. Removal of nitrobenzene in steam, followed by addition of potassium iodide (20 g.) to the residual aqueous liquor (250 c.c.), gave the corresponding 1' : 10-dimethiodide (VII; $R' = H$, $X = I$). This salt formed golden irregular plates (8.8 g.; 82%)

from water; m. p. 237—242° with effervescence (preheated bath at 200°), resolidifying and melting again at 270—275° (Found: N, 5.2; I, 46.8. $C_{18}H_{13}N_3 \cdot 2CH_3I$ requires N, 5.2; I, 47.0%).

3-Nitro-9-(3'-pyridyl)phenanthridine (II; R = NO_2 , R' = H).—Phosphorus oxychloride (200 c.c.), 5-nitro-2-nicotinamidodiphenyl (90 g.), and nitrobenzene (1.6 l.) were refluxed for 20 hours. The brown product which separated on cooling was boiled with pyridine (1 l.)—2N-ammonia (600 c.c.). **3-Nitro-9-(3'-pyridyl)phenanthridine** separated from pyridine in faintly yellow felted needles (80 g.; 94%); m. p. 250—252° (Found: C, 71.9; H, 3.8; N, 14.0. $C_{18}H_{11}O_3N_3$ requires C, 71.7; H, 3.7; N, 13.9%). The base (15 g.) was treated in nitrobenzene (400 c.c.) with methyl sulphate (4.5 c.c.; 0.95 mol.) at 170°, followed by precipitation with ether (300 c.c.). The **1'-methylmethosulphate** (86% yield) formed bulky colourless needles from methanol-ether; m. p. 210—212° (preheated bath) [Found N, 9.7; S, 7.5. $C_{18}H_{11}O_3N_3 \cdot (CH_3)_2SO_4$ requires N, 9.9; S, 7.5%].

7-Nitro-9-(3'-pyridyl)phenanthridine (II; R = H, R' = NO_2), prepared (37% yield) in a similar manner to (II; R = NO_2 , R' = H) separated in felted buff needles from pyridine; m. p. 292—293° (Found: C, 71.8; H, 3.7; N, 14.0. $C_{18}H_{11}O_3N_3$ requires C, 71.7; H, 3.7; N, 13.9%). Reaction of (II; R = H, R' = NO_2) in nitrobenzene at 170° with methyl sulphate (0.9 mol.) gave the **1'-methylmethosulphate** (III; R = H, R' = NO_2 , X = $MeSO_4$), small irregular plates from methanol-ether (78% yield); m. p. 251—253° (with previous softening) [Found: N, 9.8; S, 7.6. $C_{18}H_{11}O_3N_3 \cdot (CH_3)_2SO_4$ requires N, 9.9; S, 7.5%]. When the methyl sulphate was increased to 3 mols. the **1':10-dimethyl-dimethosulphate** (VII; R' = NO_2 , X = $MeSO_4$) was obtained, small cream plates from methanol-ether; m. p. 256—258° (with previous softening) [Found: N, 7.5; S, 11.7. $C_{18}H_{11}O_3N_3 \cdot 2(CH_3)_2SO_4$ requires N, 7.6; S, 11.6%]. The **1'-methopicate** formed bright yellow irregular needles from acetone; m. p. 300—302° (Found: N, 15.4. $C_{18}H_{11}O_3N_3 \cdot C_7H_5O_2N_2$ requires N, 15.6%).

Model Experiments with Quaternary Salts of 9-Phenylphenanthridine.—Reaction of 9-phenylphenanthridine (Morgan and Walls, J., 1931, 2451) in benzene with methyl sulphate (2 mols.) gave the **10-methylmethosulphate** (IX; X = $MeSO_4$), which separated from alcohol-ether in colourless prisms, m. p. 222—224° [Found: N, 4.0; S, 8.4. $C_{19}H_{13}N_3 \cdot (CH_3)_2SO_4$ requires N, 3.7; S, 8.4%]. The **10-methiodide** (IX; X = I) crystallised from water as well-defined bright yellow prisms which decomposed sharply at temperatures between 235 and 260°, depending on the rate of heating (Found: N, 3.7; I, 32.1. $C_{19}H_{13}N_3 \cdot CH_3I$ requires N, 3.6; I, 32.0%). The *pseudo-base* (X), precipitated from an aqueous solution of the 10-methylmethosulphate (IX; X = $MeSO_4$) by 1 mol. of N-sodium hydroxide, was extracted with ethyl acetate. It crystallised from light petroleum (b. p. 80—100°) in colourless prisms, m. p. 132—136° (Found: C, 83.8; H, 6.0; N, 5.0. $C_{20}H_{17}ON$ requires C, 83.6; H, 5.9; N, 4.9%). The *pseudo-base* (0.025 g.) dissolved in water (2 c.c.) containing N/10-hydrochloric acid (1 c.c.; 1.15 mol.), was treated with potassium iodide (0.3 g.), giving 9-phenylphenanthridine 10-methiodide (IX; X = I) identical with an authentic specimen.

9-(6'-Keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine (IV; R = H).—The yellow suspension obtained by treating a warm solution of 9-(3'-pyridyl)phenanthridine 1'-methiodide (8 g.) in water (400 c.c.) with potassium ferricyanide (20 g. in 50 c.c. water) was made alkaline by addition of 2N-sodium hydroxide (50 c.c.) and then vigorously stirred on the steam-bath for 40 minutes. Benzene (1 l.) was added to take up the product as it was formed. The red benzene layer was separated, washed with water (50 c.c.), and concentrated to 100 c.c. under reduced pressure. Addition of light petroleum precipitated **9-(6'-keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine** (4.1 g.; 70%), small buff prisms from chloroform-acetone; m. p. 211—212° (Found: C, 79.7; H, 5.0; N, 9.8. $C_{18}H_{11}ON_3$ requires C, 79.7; H, 4.9; N, 9.8%). A 57% yield of (IV; R = H) was also obtained by adding 2N-sodium hydroxide (2 c.c.) in one portion to a solution of 9-(3'-pyridyl)phenanthridine 1'-methiodide (0.4 g.) and potassium ferricyanide (1.6 g.) in 50% ethanol (40 c.c.), and refluxing the mixture for 30 minutes. The product was isolated by removing the ethanol under reduced pressure and extracting the residual suspension with benzene. Although (IV; R = H) was largely insoluble in boiling 2N-hydrochloric acid (0.13 g. in 4 c.c.), the *hydrochloride* was obtained by diluting a solution in warm concentrated hydrochloric acid (0.3 g. in 3 c.c.) with water (25 c.c.). Fawn hydrated needles separated which decomposed evolving hydrochloric acid gas above 205° (Found: C, 66.6; H, 5.3; N, 8.3; Cl, 10.3. $C_{18}H_{11}ON_3 \cdot HCl \cdot H_2O$ requires C, 66.9; H, 5.0; N, 8.2; Cl, 10.4%). The *thiopyridone* derivative was obtained by refluxing the pyridone (IV; R = H; 0.57 g.) in chlorobenzene (20 c.c.) with finely powdered phosphorus pentasulphide (1.4 g.) for 1 hour. The hot reaction mixture was filtered and the insoluble material triturated with 2N-sodium hydroxide (40 c.c.). The brown insoluble residue (0.3 g.) was collected. It crystallised from alcohol (15 c.c.) in fawn prisms (0.1 g.), m. p. 182—197° (Found: N, 9.4; S, 10.8. $C_{18}H_{11}N_3S$ requires N, 9.3; S, 10.6%).

3-Nitro-9-(6'-keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine (IV; R = NO_2).—2N-Sodium hydroxide (20 c.c.) was added to the yellow suspension obtained when 3-nitro-9-(3'-pyridyl)phenanthridine 1'-methylmethosulphate (1 g.) in water (250 c.c.) at 60° was treated with potassium ferricyanide (3 g.). The mixture was then rapidly heated to boiling. After 15 minutes the suspension was cooled. The solid product, washed free from alkali, crystallised from pyridine (25 c.c.)—methanol (50 c.c.) as well-defined light brown needles (0.5 g.; 65%); m. p. 304—305° (Found: C, 68.8; H, 4.2; N, 12.8. $C_{19}H_{13}O_3N_3$ requires C, 68.9; H, 4.0; N, 12.7%). Sublimation of the red amorphous precipitate (2.2 g.) obtained by precipitating a warm aqueous solution (40 c.c.) of 3-nitro-9-(3'-pyridyl)phenanthridine 1'-methylmethosulphate (3.2 g.) with sodium hydroxide (15 c.c. of 50% w/v. solution), at 280°/0.02 mm. yielded a yellow crystalline sublimate (0.1 g.). After crystallisation from pyridine—light petroleum, (IV; R = NO_2) was obtained, m. p. 304—305°, not depressed in admixture with an authentic sample (Found: C, 68.9; H, 4.3; N, 12.6%). Although (IV; R = NO_2) was insoluble in boiling N-hydrochloric acid (0.1 g. in 4 c.c.), the *hydrochloride* was prepared by diluting a solution in hot concentrated hydrochloric acid. The salt separated in well-defined brown prisms which evolved hydrogen chloride above 140° and melted at 303—305° (Found: N, 11.2; Cl, 9.8. $C_{19}H_{13}O_3N_3 \cdot HCl$ requires N, 11.4; Cl, 9.7%). A mixed melting point of this hydrochloride and the corresponding base showed no depression.

9-(6'-Keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine 10-Methiodide (V; X = I).—9-(6'-Keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine (4.2 g.) was treated in xylene (150 c.c.) with

methyl sulphate (6 c.c.; 4 mols.) for 30 minutes. The gum which separated on cooling was dissolved in hot water (100 c.c.). Addition of potassium iodide (9 g.) gave the *methiodide*, golden prisms from water (2.9 g.); m. p. 240–243° (decomp.) (Found: N, 6.6; I, 29.7. $C_{18}H_{13}ON_3CH_3I$ requires N, 6.5; I, 29.7%). The *methiodide* (0.4 g.) in ethanol (5 c.c.) was treated with *N*-sodium hydroxide (1 c.c.; 1.05 mol.). On dilution with water the *pseudo-base* (VI) was precipitated, forming irregular colourless prisms from aqueous alcohol (0.24 g.; 80%); m. p. 194–196° (Found: C, 75.3; H, 5.96; N, 8.9. $C_{20}H_{15}O_2N_3$ requires C, 75.5; H, 5.7; N, 8.8%). The *pseudo-base* (0.029 g.) dissolved in water (6 c.c.) containing *N*/10-hydrochloric acid (1 c.c.; 1.1 mol.) was treated with potassium iodide (0.3 g.), giving 9-(6'-keto-1'-methyl-1': 6'-dihydro-3'-pyridyl)phenanthridine 10-methiodide (V; X = I) identical with an authentic specimen.

Attempted Oxidations of 9-(3'-Pyridyl)phenanthridine 1': 10-Dimethiodide (VII; R' = H, X = I).—(a) 2*N*-Sodium hydroxide (2 c.c.) was added to a boiling solution of 9-(3'-pyridyl)phenanthridine 1': 10-dimethiodide (0.54 g.) and potassium ferricyanide (1.6 g.) in 50% ethanol (40 c.c.). After 30 minutes the alcohol was removed and the insoluble precipitate crystallised from light petroleum (b. p. 80–100°); colourless needles of 10-methyl-9-phenanthridone (VIII) separated (0.12 g.; 57%); m. p. 108–110° (Pictet and Patry, *Ber.*, 1893, **26**, 1966, give m. p. 108°) (Found: N, 6.8. Calc. for $C_{18}H_{11}ON$: N, 6.7%). If the potassium ferricyanide were omitted in the above preparation the yield of (VIII) fell to 24%. When 9-phenylphenanthridine 10-methylmethosulphate was substituted for (VII; R' = H; X = I) in the above alcoholic alkaline ferricyanide oxidation a 23% yield of (VIII) was obtained (Found: C, 80.5; H, 5.5%). The identity of this product was confirmed by a mixed melting point determination.

(b) Potassium ferricyanide (5.4 g.) was dissolved in a cold solution of the dimethiodide (VII; R' = H, X = I) in 2*N*-sodium hydroxide (40 c.c.) diluted to 1 l. with water. After two days the collected precipitated solids were extracted with ethanol (10 c.c.). The white solid which separated from the filtered extract crystallised from benzene-light petroleum as almost white prisms (0.13 g.; 45%), m. p. 206–210°, identical with 9-(6'-keto-1'-methyl-1': 6'-dihydro-3'-pyridyl)phenanthridine (IV; R = H).

(c) A cold solution of the dimethiodide (VII; R' = H, X = I) in water (500 c.c.) containing potassium ferricyanide (1.0 g.) was treated with *N*-sodium hydroxide (3 c.c.; 3 mol.). 1 c.c. of *N*-sodium hydroxide was added daily for 7 days by which time a stringy white precipitate had separated. This material (0.05 g.) was crystallised from aqueous alcohol and light petroleum giving 10-methyl-9-phenanthridone (VIII), m. p. 109–111°, mixed melting point with an authentic specimen 108–111°.

3-Amino-9-(3'-pyridyl)phenanthridine (II; R = NH₂, R' = H).—3-Nitro-9-(3'-pyridyl)phenanthridine (4 g.) in concentrated hydrochloric acid (100 c.c.) was treated at the boiling point with stannous chloride (9 g.) in concentrated hydrochloric acid (25 c.c.), refluxing being maintained for a further 45 minutes. After being allowed to cool, the yellow stannichloride was collected and dissolved in water (40 c.c.), the base was liberated with 50% sodium hydroxide and extracted with chloroform (250 c.c.). After solution in 2*N*-hydrochloric acid (charcoal) and reprecipitation, it distilled at 230°/0.05 mm. and was crystallised from methanol (40 c.c.) and water (10 c.c.). *3-Amino-9-(3'-pyridyl)phenanthridine monohydrate* formed pale yellow felted needles, m. p. 127–128° (decomp.) (Found: N, 14.7. $C_{18}H_{13}N_3 \cdot H_2O$ requires N, 14.5%). The anhydrous base formed light brown rectangular rods from benzene (1.2 g.; 33%); m. p. 165–166° (Found: C, 79.5; H, 4.6; N, 15.3. $C_{18}H_{13}N_3$ requires C, 79.7; H, 4.8; N, 15.5%). The *acetyl* derivative was prepared by heating the base (0.5 g.) and a little anhydrous sodium acetate in glacial acetic acid (5 c.c.) and acetic anhydride (5 c.c.) for 1½ hours. After sublimation at 260°/10 mm. it formed flat needles (0.3 g.); m. p. 253° (Found: C, 77.1; H, 4.9; N, 13.4. $C_{20}H_{15}ON_3$ requires C, 76.7; H, 4.8; N, 13.4%).

3-Amino-9-(3'-pyridyl)phenanthridine 1'-Methochloride (III; R = NH₂, R' = H, X = Cl).—Reduced iron (5 g.) was added as rapidly as possible to a boiling aqueous solution (40 c.c.) of 3-nitro-9-(3'-pyridyl)phenanthridine 1'-methylmethosulphate (4.27 g.), previously acidified (Congo-red) with 2*N*-sulphuric acid. After 30 minutes the mixture was filtered (charcoal) and treated with potassium iodide (5 g.). After 12 hours at 0° the solids were collected and crystallised from water (50 c.c.) and then from methanol. *3-Amino-9-(3'-pyridyl)phenanthridine 1'-methiodide* (III; R = NH₂, R' = H, X = I) formed light brown irregular plates of indefinite m. p. 180–240° (Found: C, 55.1; H, 4.3; N, 10.4; I, 30.8. $C_{18}H_{13}N_3CH_3I$ requires C, 55.2; H, 3.9; N, 10.2; I, 30.8%). The *methochloride* (III; R = NH₂; R' = H; X = Cl) formed brown rods from ethereal methanol, m. p. 256–257° (Found: N, 13.1; Cl, 11.3. $C_{18}H_{13}N_3CH_2Cl$ requires N, 13.1; Cl, 11.1%). It gave positive primary amine tests.

7-Amino-9-(3'-pyridyl)phenanthridine (II; R = H, R' = NH₂) formed a bright red stannichloride. The base separated from chlorobenzene in yellow rods (64% yield), m. p. 227–229° (Found: C, 79.5; H, 4.6; N, 15.2. $C_{18}H_{13}N_3$ requires C, 79.7; H, 4.8; N, 15.5%). The *acetyl* derivative, after sublimation at 290–300°/0.01 mm., formed felted colourless needles, m. p. 296–298° (Found: C, 76.5; H, 5.0; N, 13.4. $C_{20}H_{15}ON_3$ requires C, 76.7; H, 4.8; N, 13.4%).

7-Amino-9-(3'-pyridyl)phenanthridine 1'-Methochloride (III; R = H, R' = NH₂, X = Cl).—The *methiodide* (III; R = H, R' = NH₂, X = I) separated from water in light brown needles, m. p. 243–244° (decomp.) (Found: C, 55.4; H, 3.9; N, 10.3; I, 30.8. $C_{18}H_{13}N_3CH_3I$ requires C, 55.2; H, 3.9; N, 10.2; I, 30.8%). The *methochloride* crystallised from ethereal methanol in orange plates, m. p. 265–267° (Found: N, 12.8; Cl, 11.2. $C_{18}H_{13}N_3CH_2Cl$ requires N, 13.1; Cl, 11.1%); it gave positive tests for a primary amine.

We thank the Directors of May and Baker, Ltd., for facilities generously placed at the disposal of one of us (W. R. W.).

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[Received December 16th, 1946.]

268. A Re-examination of the Reported *m*-Nitration of Phenols and Phenolic Ethers.

By C. A. BUNTON, G. J. MINKOFF, and R. I. REED.

The products of mononitration of phenol and anisole have been analysed by several independent methods for the presence of *m*-isomerides. The conclusion has been reached that, contrary to the views of earlier investigators, the proportions in which *m*-isomerides are formed in these reactions are less than 0.1%.

ARNALL claimed (*J.*, 1924, 125, 911) that 2.1—3.3% of *m*-nitrophenol is formed when phenol is mononitrated, as it can be, smoothly, by nitric acid in acetic acid. This conclusion is supported by the claim of Griffiths, Walkey, and Watson (*J.*, 1934, 631) that 1.4—2.2% of *m*-nitroanisole is formed in the mononitration of anisole by nitric acid of *d* 1.42, by nitric acid in sulphuric acid, nitric acid in acetic acid, nitric acid in acetic anhydride, and by benzoyl nitrate.

It seems improbable that strongly *op*-orienting groups like -OH and -OR could lead to appreciable *m*-nitration, when the weakly *op*-orienting halogens do not do so. This conclusion is reinforced by the consideration that the *op*-orienting property of -OR groups, as of halogens, in aromatic substitution, is a tautomeric effect, and, unlike the inductive effect, is almost wholly a polarisability, therefore leading exclusively to *op*-substitution (Ingold and Shaw, *J.*, 1927, 2918).

Being engaged in a kinetic study of some of the special features of the mono-nitration of phenol and its derivatives we investigated these outstanding points concerning the orientation of nitration in these compounds.

Arnall and Griffiths, Walkey, and Watson based their conclusions on thermal analyses of the isolated nitration products; such methods may be unreliable unless by-products of mononitration can be removed more completely than can sometimes be established by ordinary analysis, however satisfactory apparently.

We have used three methods, applying one to phenol, one to anisole, and a third to both. These three methods give consistent results, disagreeing with those of the previous workers.

The first method, that of chromatographic adsorption, was applied to the product of the mononitration of phenol by nitric acid in acetic acid. It is possible to resolve mixtures of *o*-, *m*-, and *p*-nitrophenol by this method (cf. Strain, "Chromatographic Adsorption Analysis", Interscience Publishers, Inc., New York, 1942, p. 94); but, in application to the mononitration product of phenol, it was found that repeated adsorption of the various bands failed to reveal any trace of *m*-nitrophenol. This result, by itself, is not conclusive, as the method is difficult to standardise for small quantities of the *m*-compound, especially as the chromatogram is complicated by the presence of small amounts of derivatives of dihydroxydiphenylnitrogen oxide, which are formed during nitration of phenols.

The other method applied to phenol was an extension of Albert and Large's specific test for *m*-diamines (*Nature*, 1938, 142, 435; Albert, *J.*, 1939, 920). They observed that *m*-diamines react with glycerol and oxalic acid in the presence of zinc or calcium chloride to give the fluorescent 2 : 8-diaminoacridine. By addition of stannous chloride to their reagent they extended the test to *m*-nitroamines and *m*-dinitro-compounds.

Our further extension of this test was to convert *m*-nitrophenol into *m*-nitroaniline by heating with aminozinc chloride and ammonium chloride. As the fluorescence of 2 : 8-diaminoacridine is quenched by phenols, any unconverted phenols were removed by extraction of the product from alkaline solution. No fluorescence was observed when this test was applied to the products of nitration of phenol by nitric acid in acetic acid, although when a trace of *m*-nitrophenol was first added to the nitration product a strong fluorescence was observed. Control experiments by this method established that the proportion of *m*-nitration under our conditions was less than 0.1%.

The first method to be applied to the nitration product of anisole was that of thermal analysis; but the fractionating column used in the removal of the non-isomeric by-products of mononitration was probably much more efficient than any at the disposal of earlier workers. We investigated this mononitration under several of the conditions used by Griffiths, Walkey, and Watson, *viz.*, nitration by nitric acid of *d* 1.42, by nitric acid in sulphuric acid, and by nitric acid in acetic acid. Two methods of thermal analysis were applied to each isolated product. One was a determination of the eutectic temperature, as the second arrest-point of the cooling curve. This temperature was always that of the binary mixture of *o*- and *p*-nitroanisoles to within our experimental error (about $\pm 0.1^\circ$). The other method involved

a determination of the clearing point, followed by similar determinations after additions of pure *o*-nitroanisole sufficient, first, to lower the clearing temperature in stages to the eutectic point, and then to raise it beyond that point. In each case, the composition-temperature curve thus traced coincided (to within the accuracy of the clearing point measurements: usually $\pm 0.3^\circ$), with the curve for binary mixtures of *o*- and *p*-nitroanisoles. This curve was first traced by Griffiths, Walkey, and Watson (*loc. cit.*), whose measurements we confirm. These determinations showed that the proportions of *m*-isomeride in our mononitration products could not have been more than a small fraction of 1%.

The second method applied to the mononitration products of anisole was the fluorescence test as described for the nitrophenols. Like *m*-nitrophenol, *m*-nitroanisole is converted into *m*-nitroaniline by heating with aminozinc chloride and ammonium chloride, and the product can be converted into 2:8-diaminoacridine by the method of Albert and Large. This test gave no detectable fluorescence when applied to the nitration products of anisole, although, as with phenol, a readily detectable fluorescence was obtained on the addition of small amounts of *m*-nitroanisole to the nitration product. Control experiments on these lines give an upper limit of 0.1% of *m*-nitration in the mononitration of anisole.

Thus it is proved by three independent methods that the proportions of *m*-isomeride formed in the mononitration of phenol and anisole are lower than we could detect, and very much lower than the proportions previously reported.

EXPERIMENTAL.

Materials.—Phenol was dried and distilled under reduced pressure in an all-glass apparatus. Anisole, alkali-washed and distilled, had b. p. $154-154.5^\circ$. The nitrophenols, from British Drug Houses, Ltd., were not further purified. The *m*- and *p*-nitroanisole, after crystallisation from aqueous alcohol, and the *o*-nitroanisole, prepared from steam-distilled *o*-nitrophenol and distilled, had m.p.s agreeing with those of Griffiths, Walkey, and Watson (here given in parentheses); *o*-, 10.4° (10.45°); *m*-, 35.7° (35.5°); *p*-, 52.1° (52.0°). Acetic acid was purified with chromium trioxide and fractionated. Nitric acid (95%) was distilled successively from 100% sulphuric acid and barium nitrate.

Miscellaneous Methods.—The initial content of the lower oxides of nitrogen in the nitrating mixtures was determined by the chloramine-r method (von Eck, *Pharm. Weekblad*, 1926, **63**, 1117; see also Minkoff, Thesis, London, 1945). The nitration of phenol by nitric acid in acetic acid was carried out with excess of phenol at 20° . The nitration products were poured into excess of alkali, and unchanged phenol was removed by treatment with carbon dioxide and ether. The mixture was just acidified with acetic acid, extracted with ether, and washed. The ether was removed, and the product dried in a vacuum desiccator. The nitrations of anisole by nitric acid (*d* 1.42), by nitric acid in sulphuric acid, and by nitric acid in acetic acid, were carried out essentially as described by Griffiths, Walkey, and Watson (*loc. cit.*). The products were extracted by ether from excess of alkali. Activated alumina was used for chromatographic adsorption; mixtures of ether and benzene were used as solvent, and in order to develop the chromatogram. Nitrophenols and nitroanisoles, either reference specimens or nitration products, were converted into nitroanilines by heating with aminozinc chloride (4 parts) and ammonium chloride (1 part) at 330° for 30 hours (cf. Menz and Muller, *Ber.*, 1886, **19**, 2916). The nitroanilines were then treated by the method of Albert and Large (*loc. cit.*). Cooling curves were determined in double-walled tubes, with stirring. Clearing points were determined in narrow, thin-walled tubes with stirring by a fine glass rod.

Examples of Thermal Analyses for the Nitration of Anisole.—(a) Anisole (0.95 g.-mol.) was treated with nitric acid (*d* 1.42; 1 g.-mol.) at 45° for 5 hours with continuous stirring. The product yielded the following data: Eutectic temperature from cooling curve, -7.0° . Clearing point, $+23.3^\circ$. Deduced composition *o*/(*o* + *p*) = 43.1% (Found: C, 55.9; H, 4.7; N, 9.1. Calc. for $C_7H_7O_3N$: C, 55.0; H, 4.8; N, 9.1%). Purity by $TiCl_3$ equivalent, 99.8%). Mixtures of the product with *o*-nitroanisole gave the following results:

Calc. % <i>o</i> - after addn.	43.1	65.0	69.8	80.0	84.5
Clearing point, calc.	($+23.3^\circ$)	$+0.6^\circ$	-6.3°	-0.6°	$+2.6^\circ$
" " obs.	$+23.3^\circ$	$+0.9^\circ$	-6.1°	-0.4°	$+2.3^\circ$

(b) Anisole (0.45 g.-mol.) was treated with a mixture of nitric acid (*d* 1.42; 0.5 g.-mol.) and sulphuric acid (0.5 g.-mol.) at 45° for 4 hours with continuous stirring. The product yielded the following data: Eutectic temperature from cooling curve, -7.3° . Clearing point, $+26.2^\circ$. Deduced composition, *o*/(*o* + *p*) = 39.8% (Found: C, 55.4; H, 4.5; N, 9.9%. Purity by $TiCl_3$ equivalent, 99.9%).

Calc. % <i>o</i> - after addn.	39.8	66.6	68.1	72.8	77.1
Clearing point, calc.	($+26.2^\circ$)	-1.9°	-4.0°	-5.4°	-2.4°
" " obs.	$+26.2^\circ$	-1.9°	-4.3°	-5.5°	-2.1°

(c) Anisole (0.05 g.-mol.) was treated with 200 c.c. of nitric acid (3M) in acetic acid at 20° for 12 hours, the initial concentration of nitrous acid being 0.03M. The product yielded the following data: Eutectic temperature from cooling curve, -7.2° . Clearing point, $+33.0^\circ$. Deduced composition, *o*/(*o* + *p*) = 30.5% (Found: C, 56.0; H, 4.8; N, 9.0%. Purity by $TiCl_3$ equivalent, 100.1%).

Calc. % <i>o</i> - after addn.	30.5	47.4	64.6	71.3	75.1	84.5
Clearing point, calc.	($+33.0^\circ$)	$+20.2^\circ$	$+1.5^\circ$	-6.4°	-3.8°	$+2.0^\circ$
" " obs.	$+33.0^\circ$	$+20.4^\circ$	$+2.0^\circ$	-6.1°	-3.7°	$+2.5^\circ$

(d) Anisole (0.05 g.-mol.) was treated with 200 c.c. of nitric acid (6.3M) in acetic acid at 20° for 15 hours, the initial concentration of nitrous acid being 0.12M. The product yielded the following data: Eutectic temperature from cooling curve, -7.0°. Clearing point, +30.4°. Deduced composition, $o/(o + p) = 34.0\%$ (Found: C, 55.1; H, 4.7; N, 10.0%. Purity by TiCl_3 equivalent, 99.8%).

Calc. % <i>o</i> - after addn.	34.0	44.4	59.6	74.0	87.5
Clearing point, calc.	(+30.4°)	+22.7°	+7.6°	-4.5°	+3.8°
" " obs.	+30.4°	+23.0°	+7.5°	-4.4°	+3.6°

Synthetic mixtures. (i) A mixture of *o*- and *p*-nitroanisole of composition $o/(o + p) = 69.3\%$ gave the following results: Eutectic temperature, -7.2° (Griffiths *et al.* give the same value). Clearing point, -5.8° (interpolated from accepted values, -5.7°). Clearing point after addition of 2.0% of *m*-nitroanisole, -6.7°.

(ii) A mixture of *o*- and *p*-nitroanisole of composition $o/(o + p) = 81.8\%$ gave the following results: Clearing point, +0.9° (interpolated from accepted values, +0.7°). Clearing point after addition of 1.5% of *m*-nitroanisole, +0.6°.

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

The authors wish to thank Professor E. D. Hughes and Professor C. K. Ingold for their encouragement and interest in this work.

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[Received, January 2nd, 1947.]

NOTES.

1:9-Diaminoacridine. By (Miss) E. K. KLEIN and F. N. LAHEY.

WITH the appearance of a paper by Albert, Rubbo, Goldacre, Davey, and Stone (*Brit. J. Exp. Path.*, 1945, 26, 160) and one by Craig (*J.*, 1946, 534), in which reference was made to 1:9-diaminoacridine supplied by one of us, it becomes desirable to record the synthesis of this substance, although the work for which it was prepared has not yet been successfully concluded.

The synthesis was accomplished along standard lines. Condensation of 2-bromo-3-nitrobenzoic acid with *o*-nitroaniline in the presence of sodium carbonate without the use of a solvent gave 2:2'-dinitrodiphenylamine-6-carboxylic acid. The same product was obtained from 3-nitroanthranilic acid, *o*-bromonitrobenzene, and sodium carbonate with nitrobenzene as a solvent. Ring closure of 2:2'-dinitrodiphenylamine-6-carboxylic acid was accomplished with either sulphuric acid or phosphorus oxychloride yielding 1:9-dinitroacridone, which was readily reduced to 1:9-diaminoacridone by stannous chloride and hydrochloric acid or by sodium hydrosulphite. Reduction of 1:9-diaminoacridone with sodium amalgam gave 1:9-diaminoacridine directly, apparently without the intermediate formation of the acridin.

1:9-Diaminoacridine crystallises in yellow needles, m. p. 177°. It gives a colourless hydrochloride and is further characterised by the formation of an acetyl derivative, m. p. 250–251°.

2:2'-Dinitrodiphenylamine-6-carboxylic Acid.—(a) 2-Bromo-3-nitrobenzoic acid (5.0 g.), *o*-nitroaniline (5.0 g.), sodium carbonate (2.0 g.), and a trace of copper powder were thoroughly mixed and heated at 190–210° for 2 hours with stirring. On cooling, benzene was added, and the sodium salts were filtered off and taken up in hot water. On cooling this solution in ice, the sodium salt of 2:2'-dinitrodiphenylamine-6-carboxylic acid separated, and was filtered off and acidified with hydrochloric acid. 2:2'-Dinitrodiphenylamine-6-carboxylic acid crystallised from ethyl alcohol or xylene in yellow crystals, m. p. 246°. Yield, 1.2 g. (Found: N, 13.84. $\text{C}_{13}\text{H}_9\text{O}_6\text{N}_3$ requires N, 13.86%).

(b) A mixture of sodium 3-nitroanthranilate (4.1 g.), *o*-bromonitrobenzene (6.0 g.), sodium carbonate (1.06 g.), a trace of copper powder, and nitrobenzene (30 ml.) was refluxed for 4 hours. It was then poured into benzene and the precipitated sodium salts filtered off. The acid obtained on acidification was recrystallised from ethyl alcohol, and was identical with that recorded above. Yield, 1.6 g.

1:9-Dinitroacridone.—2:2'-Dinitrodiphenylamine-6-carboxylic acid (1.0 g.) and concentrated sulphuric acid (7 ml.) were heated on a steam-bath with stirring for 15 minutes. The dark green solution was then poured on ice. The precipitated 1:9-dinitroacridone was filtered off and heated with sodium carbonate solution and then with water. It crystallised from xylene in fluffy orange crystals, m. p. 257–258°. Yield, 0.7 g. (Found: C, 54.9; H, 2.6. $\text{C}_{13}\text{H}_7\text{O}_4\text{N}_3$ requires C, 54.7; H, 2.5%). The same compound was obtained by using phosphorus oxychloride for ring closure.

2:2'-Dinitrodiphenylamine-6-carboxylic acid (1.0 g.) was refluxed with phosphorus oxychloride (10 ml.) for 1 hour. The excess of phosphorus oxychloride was removed under reduced pressure and the dark residue treated with water and filtered off. The brown solid was boiled for 15 minutes with 5% hydrochloric acid and again filtered. It was then dissolved in boiling *N*/5-potassium hydroxide (50% alcohol). From this solution, 1:9-dinitroacridone was precipitated with dilute hydrochloric acid. Yield, 0.7 g.

1:9-Diaminoacridone.—Stannous chloride (2.5 g.) was dissolved in boiling concentrated hydrochloric acid (9 ml.) and the solution saturated with hydrogen chloride. 1:9-Dinitroacridone (1 g.) was added during 1 hour with stirring, and the boiling continued for half an hour after the addition was complete. The stannic chloride complex (1.8 g.) which settled out was filtered off, washed with ether and dissolved in 50 ml. of hot water. The solution was cooled in ice and a slight excess of ammonia (*d* 0.88) added.

The yellow precipitate was dried and extracted repeatedly with boiling absolute alcohol. Evaporation of the alcohol gave 1:9-diaminoacridone as greenish-yellow needles which did not melt up to 320°. Yield, 0.4 g. (Found: C, 68.7; H, 4.6. $C_{13}H_{11}ON_2$ requires C, 69.3; H, 4.9%).

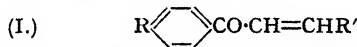
An easier method of reduction involved the use of sodium hydrosulphite. 1:9-Diaminoacridone (1.0 g.) was suspended in hot aqueous ethyl alcohol and sodium hydrosulphite added with constant stirring until a clear red solution was produced. A little hydrochloric acid was added and the solution boiled for $\frac{1}{2}$ hour. Ammonia precipitated the 1:9-diaminoacridone. Yield, 0.5 g.

1:9-Diaminoacridine.—1:9-Diaminoacridone (0.3 g.) was suspended in 30 ml. of water at 80°. Sodium amalgam (5%; 12.0 g.) was added gradually over 2 hours with stirring, and heating continued for another 2 hours. After cooling, the precipitate was filtered off, washed with water, and crystallised from 30% alcohol. Yield, 0.22 g. 1:9-Diaminoacridine formed golden-yellow crystals, m. p. 177° (Found: C, 74.5; H, 5.3. $C_{13}H_{11}N_2$ requires C, 74.6; H, 5.3%). It gave a colourless solution in hydrochloric acid. Treatment with acetic anhydride and working up in the usual way gave a diacetyl derivative, m. p. 250–251° (Found: N, 14.5. $C_{17}H_{15}O_2N_2$ requires N, 14.2%).—UNIVERSITY OF MELBOURNE. [Received, November 28th, 1946.]

The Preparation and Bacteriostatic Action of Some Aminochalkones and Related Compounds.

By D. H. MARRIAN, P. B. RUSSELL, and A. R. TODD.

KUHN, MÖLLER, WENDT, and BEINERT (*Ber.*, 1942, **75**, 711) prepared a number of analogues of the sulphonamide drugs in which a *p*-aminobenzoyl group was substituted for the *p*-aminobenzenesulphonyl residue and showed that they possessed much weaker bacteriostatic properties than sulphanilamide. Later, however, Kuhn, Möller, and Wendt (*Ber.*, 1943, **76**, 405) showed that 4:4'-diaminobenzil has from two to six times the activity of sulphanilamide against *Staph. aureus*, and has accordingly about 30 times the activity of 4:4'-diaminobenzophenone. As an aspect of certain other investigations in this laboratory it seemed of interest to prepare and test some aminochalkones and related compounds of type (I), partly in view of the above findings and partly because of the presence of the grouping $-C=C-CO-$ in a number of naturally occurring antibiotics.



4:4'-Diaminochalkone (I; R = NH_2 ; R' = *p*- $\text{NH}_2 \cdot \text{C}_6\text{H}_4$) was prepared by reduction of 4-amino-4'-nitrochalkone, itself obtained by hydrolysing *N*: ω -bis-*p*-nitrobenzylidene-*p*-aminoacetophenone (Scholtz and Huber, *Ber.*, 1904, **37**, 390). 4-Aminochalkone (I; R = H; R' = *p*- $\text{NH}_2 \cdot \text{C}_6\text{H}_4$) was prepared by reduction of the corresponding nitrochalkone with iron and acetic acid, and 4'-aminochalkone (I; R = NH_2 ; R' = Ph) by hydrolysis of *N*: ω -dibenzylidene-*p*-aminoacetophenone. *p*-Amino- ω -cinnamylideneacetophenone (I; R = NH_2 ; R' = $\text{CH}:\text{CH} \cdot \text{C}_6\text{H}_5$) and *p*-amino- ω -furfurylideneacetophenone (I; R = NH_2 ; R' = α -furyl) were prepared in similar fashion by hydrolysing the corresponding di-compounds.

The above compounds were tested against *Staph. aureus* and *Strept. haemolyticus* by a serial dilution method in glucose broth and on a synthetic medium. Although all of them showed some activity (cf. Table) it was in no case of a high order. None showed any activity against *Esch. coli* or *Pseudomonas pyocyanea*.

	Maximum dilution inhibiting			
	<i>Staph. aureus</i> .		<i>Strept. haemolyticus</i> .	
	Synthetic medium.	Glucose broth.	Synthetic medium.	Glucose broth.
4:4'-Diaminochalkone.....	1/10,000	—	1/100,000	1/10,000
4-Aminochalkone	1/5,000	—	1/50,000	1/5,000*
4'-Aminochalkone	1/10,000	—	1/10,000	—
I; R = NH_2 ; R' = $\text{CH}:\text{CHPh}$	—	—	1/5,000	1/5,000
I; R = NH_2 ; R' = α -furyl	1/10,000	1/5,000	1/5,000*	1/5,000

* Partial inhibition.

4-Nitro-4'-aminochalkone.—*N*: ω -bis-*p*-nitrobenzylidene-*p*-aminoacetophenone (3 g.; Scholtz and Huber, *loc. cit.*) was dissolved in ethanol (250 c.c.) and the solution acidified with dilute sulphuric acid. The precipitated sulphate was collected and dissolved in water, and the solution was made alkaline with sodium hydroxide. 4-Nitro-4'-aminochalkone (2.5 g.) separated as an orange-red microcrystalline powder; recrystallised from aqueous ethylene glycol monomethyl ether it had m. p. 220–221° (Found: C, 66.6; H, 4.6; N, 10.4. $C_{18}H_{15}O_3N_2$ requires C, 67.0; H, 4.5; N, 10.4%).

4:4'-Diaminochalkone.—4-Nitro-4'-aminochalkone (0.5 g.) was dissolved in acetic acid (6 c.c.) and the hot solution poured into a suspension of iron filings (2 g.) in dilute acetic acid (30 c.c. of 5%). The mixture was refluxed until all the nitro-compound had gone into solution, and then filtered hot. The filtrate, on cooling, deposited 4:4'-diaminochalkone as a crystalline powder. Recrystallised from ethanol the product formed orange needles (0.35 g.), m. p. 183–184° (Found: C, 75.5; H, 6.4; N, 11.5. $C_{18}H_{14}ON_2$ requires C, 75.5; H, 6.2; N, 11.8%); in pyridine solution it showed the blue fluorescence in ultra-violet light characteristic of 4-aminochalkones (Pfeiffer *et al.*, *Annalen*, 1925, **441**, 228), and on treatment with benzaldehyde it gave a dibenzylidene derivative, m. p. 180–181° (Found: N, 7.0. $C_{20}H_{18}ON_2$ requires N, 6.8%).

4'-Aminochalkone.—Prepared by treatment of *N*: ω -dibenzylidene-*p*-aminocetophenone with dilute sulphuric acid, 4-aminochalkone had m. p. 105–106°. Dilthey, Neuhaus, Reis, and Schommer (*J. pr. Chem.*, 1930, **124**, 81) give m. p. 108°.

4-Aminochalkone.—4-Nitrochalkone (Sorge, *Ber.*, 1902, **35**, 1068) (1 g.) was dissolved in hot acetic acid (3 c.c.) and added to a suspension of iron filings (2 g.) in dilute acetic acid (30 c.c. of 5%). The mixture was heated for 2 hours on the steam-bath, filtered, and cooled. The 4-aminochalkone which separated was recrystallised from aqueous ethanol, and thus obtained as deep yellow plates, m. p. 151–152°. Rupe and Porai-Koschitz (*Chem. Zentr.*, 1906, II, 1761), who prepared the substance by a different route, give m. p. 151°.

p-Amino- ω -cinnamylideneacetophenone.—N : ω -Dicinnamylidene-p-aminoacetophenone (Scholtz and Huber, *loc. cit.*) (3.6 g.) was dissolved in a mixture of ethanol (20 c.c.) and dilute sulphuric acid (5 c.c. of 2N), and the solution was heated on the steam-bath for 10 minutes and then cooled. The precipitated sulphate was collected and dissolved in water, and the solution was made alkaline with sodium hydroxide. The free base which separated was recrystallised from aqueous ethanol; it formed long yellow needles (2.1 g.; 83%), m. p. 159–160° (Found: C, 81.6; H, 6.3; N, 5.9. $C_{17}H_{15}ON$ requires C, 81.9; H, 6.2; N, 5.8%).

N : ω -Difurfurylidene-p-aminoacetophenone.—p-Aminoacetophenone (2.7 g.) and furfuraldehyde (3.85 g.) were dissolved in ethanol (25 c.c.), and cooled to 0°, a solution of potassium hydroxide (1.08 g.) in ethanol (20 c.c.) was added, and the mixture was allowed to stand overnight. The crystalline material which separated was recrystallised from ethanol. The compound formed yellow needles (4 g.), m. p. 103–104° (Found: C, 74.6; H, 4.4; N, 5.1. $C_{18}H_{13}O_5N$ requires C, 74.2; H, 4.5; N, 4.8%).

p-Amino- ω -furfurylideneacetophenone.—N : ω -Difurfurylidene-p-aminoacetophenone was hydrolysed with sulphuric acid in the normal manner (see above). Recrystallised from water, the compound formed yellow needles, m. p. 113–114° (Found: C, 72.9; H, 5.3; N, 6.6. $C_{18}H_{11}O_5N$ requires C, 73.2; H, 5.2; N, 6.7%).

The microbiological assays were carried out in the laboratories of Glaxo Laboratories Ltd., to whom our thanks are due. Grants from the Agricultural Research Council are gratefully acknowledged.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [Received, December 19th, 1946.]

Some New Condensation Products of Ethyl cyclopentanone-2-carboxylate with Aromatic Amines.

By H. C. BARANY and M. PIANKA.

FOR the formation of substituted anilides of cyclopentanone-2-carboxylic acid a slight modification of the method of Blount, Perkin, and Plant (*J.*, 1929, 1983) was employed. 0.025 Mole of the amine was gradually added to 0.1 mole of boiling keto-ester containing 0.5 c.c. of pyridine. The mixture was boiled for 2 minutes, cooled, and allowed to crystallise. In some cases crystallisation set in only after some days. Crystals were filtered off, washed with cold ethanol, and treated with a 4% sodium hydroxide solution to free them from any anil formed. The solution was filtered and acidified with dilute acetic acid. The precipitate was filtered off, dried, and recrystallised from ethanol or amyl alcohol. The condensation products prepared are shown in the table opposite.

The condensation products were coupled in alkaline solution with phenyldiazonium chloride, yielding dyes insoluble in water, but soluble in lower alcohols, acetone, and ether, and ranging in colour from lemon-yellow to orange-red.

On application of the film strip test (Weissberger and Porter, *J. Amer. Chem. Soc.*, 1943, **65**, 1502), consisting of immersing an exposed strip of photographic film in a 3% sodium carbonate solution of equal weights of the anilide to be tested and *NN*-diethyl-p-phenylenediamine hydrochloride for 5 minutes, rinsing with water, and bleaching out the silver and silver halide, coloured strips ranging from greenish-yellow to light brown were obtained.

Mr. Edgerton and the Directors of Dufay-Chromex Limited are thanked for permission to publish this note and Mr. H. D. Murray and Mr. B. Gluck for suggesting the use of the anilides in colour photography.—RESEARCH LABORATORIES, DUFAY-CHROMEX LIMITED, ELSTREE, HERTS. [Received, December 9th, 1946.]

Amine.	M.p. of condensation product.	Formula.	Analysis.					
			Found (%).			Required (%).		
			C.	H.	N.	C.	H.	N.
Aniline	104°*		—	—	—	—	—	—
Benzidine	charring >270†		—	—	—	—	—	—
<i>o</i> -Toluidine	96—96		—	—	—	—	—	—
<i>m</i> -Toluidine	98—99		—	—	—	—	—	—
<i>p</i> -Toluidine	118—119		—	—	—	—	—	—
<i>p</i> -Chloroaniline	115	$C_{13}H_{15}O_2N$	{71.79	6.93	6.45	—	—	—
<i>p</i> -Bromoaniline	132	$C_{12}H_{12}O_2NCl$	{71.83	6.98	6.45	—	—	—
2:4-Dichloroaniline	156	$C_{12}H_{12}O_2NBr$	{71.81	7.01	6.43	—	—	—
2:5-Dichloroaniline	104	$C_{12}H_{11}O_2NCl_2$	60.59	5.09	5.90	71.88	6.91	6.45
<i>o</i> -Anisidine	155—156	$C_{13}H_{15}O_3N$	50.96	4.31	4.98	60.64	5.05	5.89
<i>p</i> -Anisidine	136—137	$C_{13}H_{15}O_3N$	{52.90	4.06	5.12	51.09	4.26	4.96
2:5-Diethoxyaniline	95	$C_{15}H_{17}O_4N$	{52.92	4.04	5.10	52.94	4.04	5.15
<i>p</i> -Aminoethyl benzoate	273—274	$C_{13}H_{15}O_3N$	{67.05	6.50	6.05	66.94	6.44	6.01
α -Naphthylamine	162	$C_{14}H_{13}O_2N$	66.10	7.18	4.92	65.98	7.22	4.81
<i>NN</i> -Diethyl- <i>p</i> -phenylenediamine	210—211	$C_{18}H_{21}O_2N_2$	65.56	6.09	5.14	65.46	6.18	5.09
<i>o</i> -Phenylenediamine	158—159	$C_{18}H_{15}O_2N_2$	{75.84	5.97	5.60	75.90	5.93	5.53
<i>p</i> -Phenylenediamine	217—218 (decomp.)	$C_{18}H_{15}O_2N_2$	{75.82	6.02	5.58	70.06	8.05	10.22
	200 (decomp.)	$C_{18}H_{20}O_4N_2$	70.02	8.07	10.32	—	—	—
			{65.69	6.10	8.63	65.86	6.09	8.54
			{65.76	6.11	8.65	—	—	—
			{65.81	6.13	8.62	—	—	—

Except for the condensation products of ethyl cyclopentanone-2-carboxylate with *o*-, *m*-, and *p*-phenylenediamine, which were recrystallised from amyl alcohol, all the anilides were recrystallised from ethanol.

Melting points are uncorrected.

* Blount, Perkin, and Plant, *loc. cit.*

† Linstead and Wang, *J.*, 1937, 807.

X = halogen.

Some Applications of Surface Chemistry to Problems in Colloid Science.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON FEBRUARY 6TH, 1947,
AND AT THE UNIVERSITY COLLEGE OF NOTTINGHAM ON MARCH 18TH, 1947.

By A. E. ALEXANDER, B.Sc., M.A., Ph.D.

SURFACE chemistry, or surface physical chemistry as it might more appropriately be termed, is concerned with the study of interfaces, generally those of macroscopic area. The field is now an extensive one and for that reason this lecture will be restricted to the three interfaces air-water, oil-water, and solid-liquid, which are of particular relevance to typical colloidal systems such as foams, emulsions, proteins, pastes, bacteria, etc. One important aspect, namely, reactions at interfaces, was surveyed by Professor Rideal in his recent Liversidge Lecture.¹

In order to appreciate the results an outline of the principal experimental techniques, particularly those of more recent development, is desirable.

The study of insoluble monolayers at the air-water surface, based upon the classical work of Langmuir and of Adam, and later extended by Rideal, Harkins, and many others, undoubtedly forms the basis of our present knowledge of surface phenomena. The principal measured quantities of the monolayer are its surface pressure, Π ($\Pi = \gamma_{\text{water}} - \gamma_{\text{film}}$), its surface potential, ΔV ($\Delta V = V_{\text{water}} - V_{\text{film}}$), and its mechanical properties (viscosity and elasticity), all measured as a function of the molecular area (A).

Several techniques for the automatic recording of Π - A and ΔV - A curves have been devised; ² these are particularly useful for examining phase changes and stability ranges in condensed monolayers. A simple film balance recently described ³ makes the accurate study of Π - A curves readily accessible.

Condensed monolayers on water can frequently be transferred to a solid surface by a simple dipping process, and layers many molecules thick have thus been built up. These "multi-layers," or "built-up films" as they are termed, find a number of applications, particularly where very thin layers of known thickness are required.⁴

Oil-water interfaces are clearly more directly related to emulsion and biological systems than are air-water interfaces, but the study of insoluble monolayers there has proved much less amenable. However, accurate Π - A curves can now be measured by means of a technique based upon the ring method for surface tension.⁵ Some studies of "interfacial potentials" (ΔV) and of the mechanical properties of such films have also been carried out.⁶

With adsorbed films at mobile interfaces recent interest has been largely concerned with the study of rates of adsorption and desorption. Slow changes can readily be followed by any of the standard methods for boundary tension; for rapid adsorptions the oscillating-jet method recently developed and extended to oil-water interfaces,⁷ and a method utilising surface potentials,⁸ are available.

As regards adsorbed films at the solid-liquid interface, mention may be made of a recent simple method for surface-area determination of fine powders. It merely involves using long-chain polar compounds, in organic media, as adsorbates, and determining the concentration before and after adsorption by spreading as a monolayer on a film balance.⁹ The adsorption isotherm and the saturation uptake, giving the specific surface, are obtained in the usual manner, a value of 20 Å.² per long-chain molecule being assumed at the saturation point.

Having outlined the basic techniques, it is now possible to survey those results which bear directly upon a number of problems in colloidal systems.

The first problem considered will be the proteins, or rather certain aspects connected with them. In addition to their obvious biological importance proteins are common stabilising agents for foams and emulsions, an aspect discussed in more detail below.

Despite their solubility in water, proteins can usually be spread quantitatively as homogeneous monolayers at both air-water and oil-water interfaces. Such monolayers have been extensively studied in the hope of throwing some light upon the structure of the native protein molecule, as well as upon the formation and structure of protein membranes. In addition, attempts have been made recently to determine the molecular weight of proteins from Π - A curves of monolayers in the gaseous state.¹⁰ The technique here is not simple, since measurements have to be made at very large areas and therefore at minute surface pressures. As an illustration of the method, egg albumin has given values of 40,000¹⁰ and 44,000,¹¹ close to the

accepted value for this protein in solution. In the case of haemoglobin the "surface molecular weight" of 12,000 at the air-water interface indicates splitting into some five or six fragments (cf. results for haemoglobin at an oil-water interface, mentioned below).

At the air-water interface the monolayers from widely different proteins are remarkably similar as regards their Π - A curves, although their viscosity and elasticity characteristics may vary considerably. Spreading appears to be accompanied by the complete loss of solubility and, in general, of enzymatic and specific immunological properties, indicating very radical and irreversible changes in structure. Such changes are believed to arise from the polypeptide chains in the protein molecule, originally coiled in some way so as to give a corpuscular form, being unrolled and reorientated on the surface by the action of the very asymmetric field at the interface. Other notable features are the ready formation of two-dimensional elastic gels showing marked hysteresis, and the ease of compression to areas (often less than 10 Å.² per residue) which appear too small for a close-packed monolayer. Oil-water interfaces of high interfacial tension show very similar phenomena, but as the tension is reduced the protein molecules appear to suffer less drastic changes (see also below).

Early speculations concerning the molecular structure of protein monolayers were not very conclusive, largely because of insufficient knowledge of the behaviour of linear polymers at interfaces, and of the bonding between the polar groups present, particularly between $>C=O$ and $H-N<$ in the main chain, and groups such as $-COO^-$ and NH_3^+ in the side chains. A recent study¹² of monolayers of synthetic linear polymers of known structure (*e.g.*, poly-acrylates, poly-methacrylates, nylons, etc.) has enabled the contribution from the first of the above factors to be assessed much more precisely. Collapse of such films, and probably therefore of proteins too, leads to the formation of a thickened layer or overfilm rather than to a looping of the chains beneath the surface as previously believed by some workers. It may be mentioned that films built up by the multilayer technique from monolayers of amorphous polymers have been shown by electron diffraction to possess a much higher degree of order than those formed by the more usual methods.¹³

The interaction between the polar groups in proteins, in particular the extent of hydrogen bonding between the $>C=O$ and $H-N<$ groups of adjacent chains, has been investigated by comparing monolayers of simple paraffin-chain compounds containing the $-CO\cdot NH-$ group (*e.g.*, acetamides, ureas) with the analogous esters and ketones, where intermolecular hydrogen bonding is impossible.¹⁴ The replacement of $-O-$ or $-CH_2-$ by $-NH-$ brings about striking changes in monolayer properties, and the conclusion is reached that intermolecular hydrogen bonding is certainly of major importance in protein monolayers. This approach enables reagents known to bring about changes in native proteins (*e.g.*, urea) to be assessed as regards their action upon the keto-imino-hydrogen bonds.

Turning now to two closely related classical colloidal systems, namely, foams and emulsions, the principal problems arising are as follows: the adsorption of the stabilising agent during the dispersion process, the structure of the adsorbed film and its importance in relation to the gross stability, and finally the desorption of stabilising agent as re-aggregation occurs. Surface chemistry has been able to supply considerable information about all of these problems, although it must be confessed that the picture is by no means complete.

The rate of adsorption at an air-water interface, which is usually followed by surface-tension measurements, is found to occur much more slowly than predicted by classical diffusion theory.¹⁵ In the case of soaps and dyes, for example, the ratio of the calculated to the observed rate may be 10^6 or more. The hindrance to diffusion has usually been ascribed to an electrostatic potential barrier at the surface, arising from the presence of the adsorbed layer of long-chain ions, but the fact that similar anomalies arise with un-ionised compounds (*e.g.*, β -phenyl-propionic acid at pH 2) shows that this factor is certainly not the major one. The rate of attainment of equilibrium is accelerated by the presence of other surface-active substances, by insoluble monolayers, and by replacing the air by an oil phase.⁸ Such experiments suggest that the main factor in these slow diffusions arises from the steric hindrance which a long hydrocarbon chain encounters when endeavouring to penetrate a comparatively close-packed monolayer. Anomalously slow adsorption of long-chain polar compounds can also occur from an oil phase to an aqueous interface, a phenomenon closely related to their well-known tendency to aggregate in organic media.¹⁶

Desorption, even with molecules of not particularly complex structure (*e.g.*, β -phenyl-propionic acid), appears to be an equally hindered process, although little has been done on this aspect, particularly at oil-water interfaces. Compression of a film adsorbed at an air-

water interface may even lead to the adsorbate separating out on the surface as a crystalline or liquid aggregate.¹⁷

The structure of the stabilising film in foams and emulsions, in particular whether the thickness is uni- or multi-molecular, can frequently be inferred indirectly from surface studies. In the case of water-soluble compounds (*e.g.*, soaps, and the lower fatty acids or alcohols) an equation of state can be deduced from the study of homologous longer-chain compounds which form insoluble monolayers, and this enables the adsorption, if confined to a monolayer, to be calculated at both oil-water and air-water interfaces.¹⁷ The values thus calculated for the two most accurately studied compounds are seen from the data below to agree closely with the experimental ones obtained by McBain and his co-workers using the microtome method.

Solute.	Calc.	Adsorption.	Exptl.
β -Phenylpropionic acid	8.3×10^{-8} g./cm. ²	7.7×10^{-8} g./cm. ²	
Laurylsulphonic acid	5.7×10^{-10} g.-mol./cm. ²	$5.2-5.7 \times 10^{-10}$ g.-mol./cm. ²	

The conclusion is therefore drawn that in foams, and by analogy also in emulsions (oil-in-water type), stabilised by water-soluble soaps, the interfacial films are no more than unimolecular in thickness, and are in a highly compressed gaseous (and hence fluid) state, with molecular areas of *ca.* 30 Å.² for simple straight paraffin-chain derivatives. Stabilisation arises chiefly from the marked reduction in the surface energy of the system, although other factors, particularly the surface viscosity of the adsorbed film, also play a part. The close connection between the lowering of interfacial tension and emulsion stability is shown particularly by systems stabilised by "interfacial complexes" formed between a water-soluble soap and organic compounds containing hydroxyl or amino-groups (*e.g.*, cholesterol, long-chain amines) dissolved in the oil phase.¹⁸ The study of oil-water insoluble monolayers shows that in the case of stable oil-in-water emulsions the oil phase will be effectively displaced from the interface by the adsorbed monolayer of stabiliser.⁸

With the heavy-metal or oil-soluble soaps (*e.g.*, magnesium oleate) which stabilise the water-in-oil type of emulsion, the monolayers in equilibrium with the solid soap phase are also in a fluid, gaseous state, but the equilibrium spreading pressures are very much less than in the case of water-soluble soaps, which effectively rules out any stabilisation by a monolayer. The spontaneous formation of visible rigid films by reaction between heavy-metal cations and fatty acids at an oil-water interface indicates stabilisation by solid particles, in agreement with the observation that stable water-in-oil emulsions invariably contain solid soap.¹⁹

Protein solutions in contact with air-water and oil-water interfaces readily give rise to tough visible "skins", a phenomenon first recorded by Ascherson over a century ago, and still very imperfectly understood. In the case of an air-water interface this "surface denaturation" continues until all the protein present has been removed as a coagulum practically devoid of surface activity. At oil-water interfaces, the rate and the extent of these surface changes diminish with decreasing interfacial tension.²⁰ For example, if hæmoglobin is desorbed (by changing the pH) from the surface of a fine emulsion stabilised by sodium cetyl sulphate its molecular weight is unaffected but its ultracentrifuge dissymmetry coefficient has increased from 1.16 to 1.33, indicating some, but not complete, unfolding of the molecule.²¹

The behaviour of monolayers of proteins at air-water and oil-water interfaces suggests very strongly that proteins stabilise foams and emulsions by the formation of multimolecular films or skins rather than by a monolayer, these conferring mechanical protection.

The question of elasticity in adsorbed films is important in relation to the question of thermodynamic stability of foams and emulsions. Monolayers only show elasticity when in the condensed state, and from the study of equilibrium spreading pressures of crystals it would appear that all *condensed* monolayers are unstable with respect to their bulk phase. Accordingly, if an *adsorbed* film exhibits elasticity (as with protein or saponin solutions, and with heavy-metal soaps formed by metathesis at an interface), it would seem probable that its structures is multimolecular rather than unimolecular, and that the system is not in thermodynamic equilibrium.

Mention may be made in passing of Hardy's technique for studying foam stability by measuring the life-time of an air bubble liberated beneath an insoluble monolayer. Appreciable stabilisation is only obtained with coherent monolayers (expanded or condensed), and the stability decreases in the highly condensed state where the monolayers become unstable.²²

Passing now to a consideration of pastes (concentrated dispersions of finely divided solids in a liquid continuum), some recent work⁹ has shed much light upon the influence of surface-

active substances upon their macroscopic properties, such as flow behaviour and sedimentation volume. The adsorption upon polar powders such as sodium nitrate, using paraffin-chain compounds with different polar groups, in benzene or organic solution, was found to be in the following order $\cdot\text{NO}_2 > \cdot\text{CO}_2\text{H} > \cdot\text{OH} > \cdot\text{C}=\text{O}$. Parallel measurements of the coefficient of friction between large crystals showed that the friction was lowered in the same order. With increasing adsorption the ease of flow increases and the sedimentation volume decreases. Adsorption in these systems takes place with the polar groups of the adsorbate molecules oriented towards the polar surface of the crystal, and the hydrocarbon chains extending into the organic liquid. This outer surface of hydrocarbon reduces the interaction between the polar crystals and leads to the observed changes in macroscopic properties.

Finally, brief reference may be made to the application of surface studies to problems of a biological nature. Two examples only will be considered here, although others have been studied in this way (e.g., the mechanism of fat absorption).²³

Hexylresorcinol is a well-known anthelmintic for *Ascaris* and other intestinal worms. *In vitro* tests showed its activity to be considerably affected by the presence of bile salts or other soap-like substances, low concentrations generally producing some activation, but very high ones complete inhibition. Measurement of the surface activities of the various mixtures showed that the inhibition arises from the colloidal soap micelles, which form at the higher soap concentrations, competing with the biological surface for the fixed amount of drug.²⁴ The activation produced by low soap concentrations is related to the increased surface activity of the mixture, leading to an increased rate of penetration.

Similar conclusions have been found to apply to the bactericidal action of phenols in the presence of soaps. Rideal-Walker tests, and measurement of the rates of killing, show that the bactericidal activity increases up to the point where soap micelles start to form, and thereafter decreases.²⁵

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OBITUARY NOTICE.

EDMUND BRYDGES RUDHALL PRIDEAUX.

1878—1946.

EDMUND BRYDGES RUDHALL PRIDEAUX was born in Barbados and educated at the Auckland Grammar School and Canterbury College, New Zealand University. His education, following the tradition of his family, was mainly classical; although he devoted himself to science he never lost his love of the classics and throughout his life would turn to them for solace and inspiration.

In 1901 he came to London but moved, in 1906, to the Heriot Watt College, Edinburgh, and thence, in 1909, to Liverpool University. Professor Donnan writes: "I had the great pleasure of welcoming Dr. E. B. R. Prideaux when he came to work in the Muspratt Laboratory of Physical and Electro-chemistry after having spent a year or two of research in the laboratory of Sir William Ramsay at University College, London. As a senior research worker of ability and experience he was a great source of strength to us in Liverpool and he made very valuable contributions to the research output of the laboratory. His lectures to the senior students on physico-chemical calculations were highly appreciated. I think I may claim the honour of having directed his attention to the special study of ionic equilibria in solutions and the various types of electrical potential differences associated therewith.

"Dr. Prideaux was a quiet, thoughtful, and scholarly man of science, and I have the happiest recollections of my association with him during those Liverpool years. He was one of a number of excellent men from New Zealand, including Denham, Stubbs, and Farrow, who contributed greatly to the success of the Muspratt Laboratory and the advance of physical chemistry."

In 1913 Prideaux moved to the Battersea Polytechnic and, in the following year, to the University College of Nottingham. His output of research was increasing rapidly but it received a check due to the outbreak of war. Much of his time was spent in assisting the National Shell-filling Factory at Chilwell and in preparative organic chemistry in connection with the production of β -eucaine. With the end of the war came the great influx of ex-service students, and in their interests he spent himself unstintingly.

Professor Kipping writes: "Dr. Prideaux was deeply imbued with the true scientific spirit which alone enabled him to accomplish the work for which he was distinguished in spite of his conscientious and painstaking preoccupation with his academic duties and, often also, with very inadequate apparatus.

"Although quiet and reserved in unfamiliar surroundings, with some of the attributes of a recluse, he was a kind and genial man and an interesting companion with broad and well informed views and decided opinions on many subjects. Some of the less desirable qualities which so often determine worldly success were, however, entirely foreign to his character; he was too altruistic, lacking in self-assertion and prone to neglect opportunities for his own advancement. It was, doubtless, for this reason that he failed to attain the higher rank in his profession to which he was entitled.

"He was not only, during many years, an accomplished member of my staff but also a highly valued friend."

As a research worker Prideaux was remarkable for his versatility; scarcely a single branch of chemistry escaped his attention, and he published some 90 papers in scientific journals apart from articles on scientific and educational topics. After obtaining the M.A. degree of New Zealand University he completed a research on Kauri resin and was awarded the B.Sc. degree. He continued to work on resins at the Imperial Institute in London in 1902, but then, under Ramsay, turned his attention to fluorine. He discovered the compounds BrF_3 , TeF_6 , and SeF_6 . This work gained him the D.Sc. degree of London University. Fluorine continued to interest him throughout his life, and some 12 of his papers are devoted to this element and its compounds with selenium, tellurium, zirconium, and rubidium.

Phosphorus and its compounds also interested Prideaux, and his electronic formulation of phosphorus pentachloride received wide publicity. He published many papers on phosphoric and boric acids and was a pioneer in the use of modern indicators, and of the hydrogen and quinhydrone electrodes, and, in general, in the practical applications of the electrolytic dissociation theory. With A. T. Ward he devised the first "universal" buffer solution.

The dissociation constants of phenols and of alkaloids, the separation and estimation of pyridine and ammonia, the analysis of nitrotoluenes, benzoates, and salicylates, the spectro-

photometric examination of dyes and indicators, photo-synthetic phenomena in sea water, diffusion and membrane potentials, the corrosion of cement; these and other topics are evidence of the catholicity of Prideaux's tastes in research. In collaboration with F. O. Howitt he contributed valuable papers on the electrophoresis and isoelectric points of proteins and the kataphoresis of insulin. His theoretical papers helped the development of views on molecular structure.

Prideaux wrote several books: "The Theory and use of Indicators," "Problems in Physical Chemistry," and "A Survey of English Elementary Education." He was the author of the volume "Phosphorus" in Newton Friend's Text Book of Inorganic Chemistry, and joint author, with Herbert Lambourne, of the volume "Nitrogen," and with F. C. Laxton of "A Laboratory Course in Elementary Chemistry." He was, moreover, one of the pioneers in popular broadcast talks on scientific topics.

In 1908 Prideaux married the elder daughter of Rowland Bramwell, Esq., of Auckland, New Zealand. In 1946 he resigned his post as Reader in Physical and Inorganic Chemistry in the University College of Nottingham and, in recognition of his services, was awarded the title of *Lector Emeritus*. He then settled, with his wife and daughter, in his home at Canford Cliffs, Bournemouth, hoping to carry on his researches unhampered by the academic duties to which so much of his life had been devoted. The repose he had so richly earned by a life of labour was, however, denied him; he died on the 8th of May, 1946. His memory lives in the hearts of the students and friends who knew and valued him.

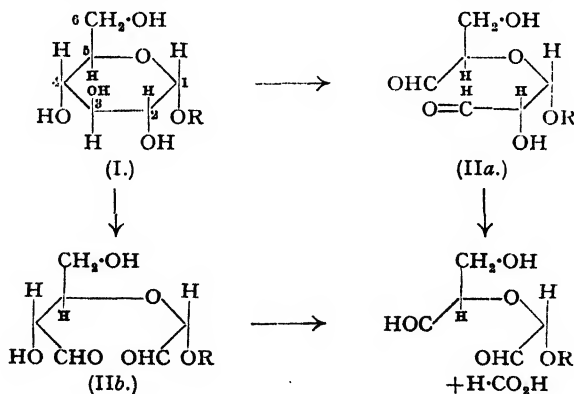
B. D. SHAW.

269. Oxidation of Carbohydrates by the Periodate Ion.

By T. G. HALSALL, E. L. HIRST, and J. K. N. JONES.

The oxidation, with salts of periodic acid, of the methylglycosides of the hexose and pentose sugars and of the disaccharides has been investigated. Sugar derivatives containing hydroxyl groups on each of three adjacent carbon atoms are oxidised with the formation of 1 mol. of formic acid, and conditions have been established for the quantitative estimation of the formic acid. Methyl hexo- and pento-pyranosides and the methyl glycosides of maltose and cellobiose give rise quantitatively to 1 mol. of formic acid, but reducing sugars, methylglycosides of the uronic acids, and methylhexofuranosides yield acidic material equivalent to more than 1 mol. of formic acid per mol. of sugar. The causes of this continued oxidation are discussed.

THE observation by Hudson and Jackson (*J. Amer. Chem. Soc.*, 1936, **58**, 378; 1937, **59**, 994), that the α - and β -methylglucosides yield on oxidation with periodic acid a dialdehyde together with 1 mol. of formic acid, affords a possible method of estimating the number of end groups present in a polysaccharide which has terminal groups of the type (I), provided that the non-terminal groups are such that they do not yield formic acid. Such a method should therefore be applicable to a wide range of polysaccharides, including starch, cellulose, and glycogen, which possess chains of 1:4-linked hexopyranose residues, but hitherto attempts to make use of this procedure have encountered difficulty in that the oxidation is not arrested at



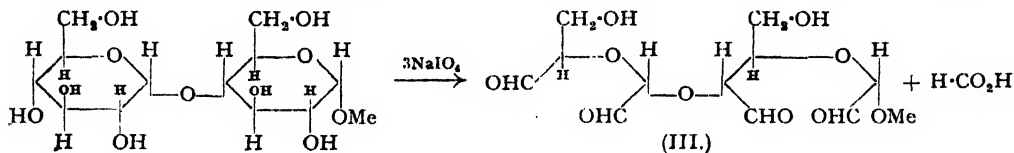
the stage when 1 mol. of formic acid has been liberated from the terminal group (Davidson, *J. Textile Inst.*, 1941, **32**, T, 109). Nevertheless the reaction has been used successfully in other

ways in the study of polysaccharides. For example, the stepwise degradation of laminarin, which consists of 1 : 3-linked residues, has been described by Barry (*Nature*, 1943, 152, 538) and by Dillon (*ibid.*, 1945, 155, 546), and attempts have been made to estimate the formaldehyde produced from the reducing end of the chain in starch dextrins (Caldwell and Hixon, *J. Biol. Chem.*, 1938, 123, 595).

In view of our interest in methods for estimating end groups in polysaccharides we decided to undertake a more detailed survey of the conditions requisite for the prevention of over-oxidation and thus facilitate the development of a method of estimation which would possess many advantages over the present available techniques. This was all the more necessary in that we had found in the course of experiments on plant gums, in which we had hoped to remove certain side chains with the aid of periodic acid, that difficulties due to over oxidation were encountered.

As a preliminary, therefore, to the application of the periodate method of oxidation to the polysaccharides, model experiments were carried out with simple sugars containing groups similar to those present in polysaccharides. These included α -methylglucopyranoside, α -methylgalactopyranoside, α -methylmannopyranoside, α -methyl-*D*-mannofuranoside, β -methyl-maltoside, β -methylcellobioside, β -methyl-*L*-arabopyranoside, α -methyl-*D*-xylopyranoside, amygdalin, mannitol, lactose, lactal, and the methyl ester of α -methyl-*D*-galacturonoside. Control experiments with formic acid, ethylene glycol, and oxalic acid were also carried out.

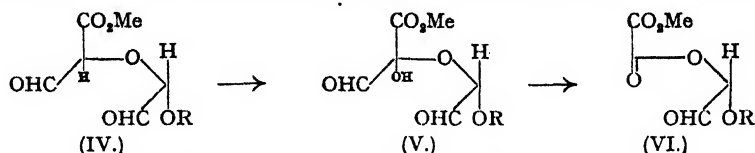
It was our aim to estimate small amounts of formic acid, and this we found practicable only when the excess of periodate had been destroyed by the addition of ethylene glycol with the resultant formation of formaldehyde and sodium iodate, both of which were without action on methyl-red used as indicator for the titration of the formic acid. Sodium periodate slowly destroys formic acid, and the estimated amount of the latter may be low unless precautions are taken. It was found, however, that the oxidation of formic acid is considerably slowed down in the presence of sodium iodate, and, as this substance is always formed by reduction of the periodate, loss of formic acid during the period of oxidation is negligible. Sodium periodate gives satisfactory results for the oxidation of small amounts of methylhexopyranosides and pentopyranosides, all of which on oxidation give 1 mol. of formic acid. On the other hand when this reagent is applied to the methylglycosides of the reducing disaccharides oxidation proceeds beyond the stage represented by (III), and ultimately considerably more than 1 mol. of formic acid is produced per mol. of methylglycoside. The rate of production of formic acid is much slower, however, after the liberation of 1 mol., but with a large excess of sodium periodate as oxidising agent there is not an easy differentiation between the two stages of the reaction.



We therefore examined other salts of periodic acid which had lower solubility and would provide reaction solutions of lower acidity. Most of the salts examined were unsatisfactory since they possessed either basic or strongly acidic characteristics. Potassium metaperiodate, however, is only very slightly soluble in water and gives a solution having a pH of about 4. Using this salt and keeping the concentration of formic acid produced to a low value (*ca.* 10 mg. per 100 c.c.), we were able to obtain consistent and reliable figures for the amount of formic acid produced. This lowering of concentration of the periodate ion, however, considerably reduces the rate of reaction, and instead of being complete in 6 hours it now requires 150 hours at 15°. On oxidation with this reagent the methylglycosides of (a) the hexose, (b) the pentose sugars, and (c) the reducing disaccharides gave normal amounts of formic acid. The methylglycosides of uronic acids and of hexofuranosides underwent further oxidation with the formation of additional amounts of acidic material. Similar behaviour was shown by reducing sugars.

The oxidation of the glycosides of the uronic acids has been the subject of previous publications. Huebner, Lohmar, Moore, and Link (*J. Biol. Chem.*, 1945, 159, 502) demonstrated that, in the oxidation of zinc borneol glucuronoside, more than 1 mol of acid was produced per mol. of glucuronoside and that one of the reaction products was bornyl formate. They suggested that the uronic acid residue, after undergoing oxidation with the formation of formic acid and the dialdehyde (IV), was further oxidised by the periodate. The first step in this oxidation, it was suggested, was the oxidation of the active hydrogen situated on the carbon atom between

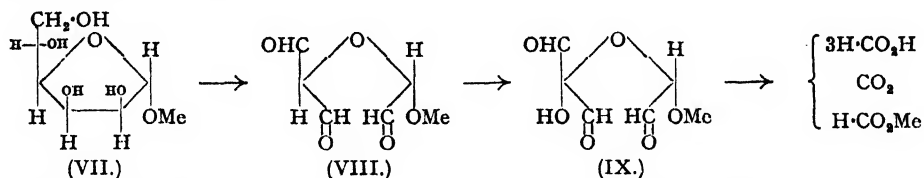
two carbonyl groups to a hydroxyl group (V). This would result in the formation of a substance which in its hydrated form contains hydroxyl groups on adjacent carbon atoms and would



undergo further oxidation with periodate with the formation of an ester of oxalic acid (VI). Once this stage had been reached the ester, which would be unstable in water, could hydrolyse to oxalic acid and a product which could then undergo further oxidation to formic acid and an ester of formic acid.

The stage in which the aldehyde (IV) is converted into the α-hydroxy-aldehyde (V) has been investigated by Sprinson and Chargaff (*J. Biol. Chem.*, 1946, **164**, 443). These workers demonstrated that substances such as malonic acid and its derivatives—substances which contain a hydrogen atom combined to a carbon atom situated between two carbonyl groups $\left(\begin{array}{c} \text{O} & \text{H} & \text{O} \\ \parallel & | & \parallel \\ -\text{C} & -\text{C} & -\text{C}- \end{array} \right)$ —are all capable of being oxidised to the corresponding hydroxy-compound which may then undergo further oxidation [cf. the work of Neuberger (*J.*, 1941, 47) on the oxidation of ethyl *N*-benzoylglucosamate].

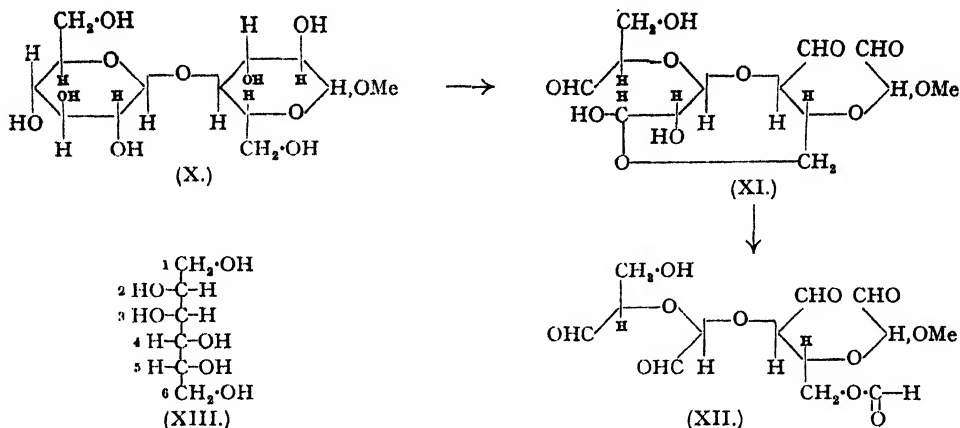
We have found that whenever this secondary type of oxidation occurs free iodine is ultimately produced and the amount of acid in the solution falls. The mode of origin of the iodine is obscure, but the simplest explanation would be to ascribe its formation to the well-known reaction between sodium iodide and sodium iodate in acid solution, the sodium iodide arising in turn from reduction of sodium iodate during oxidation on the activated carbon atom. A typical example of the grouping which undergoes further oxidation, with liberation of free iodine, is shown in (VIII) which is the intermediate product obtained by the periodate oxidation of α-methylmannofuranoside (VII). Attack at the activated hydrogen would yield (IX) which would readily undergo further oxidation giving 3 mols. of formic acid, 1 mol. of methyl formate, and 1 mol. of carbon dioxide.



The rate of oxidation and rate of formation of formic acid varies with the configuration of the glycoside. Those glycosides, such as the arabo-, galacto-, and manno-pyranosides, which contain *cis*-hydroxyl groups, are oxidised relatively quickly, whilst those glycosides which contain *trans*-hydroxyl groupings, such as the glucopyranosides, are oxidised more slowly (cf. "Organic Reactions", Vol. 2, p. 353, Wiley, New York). The presence of *cis*-hydroxyl groups, however, is not the only factor which decides the rate of formation of formic acid. This is dependent also upon the rate of oxidation of the α-hydroxy-aldehyde, which is a comparatively slow reaction. Furthermore, the methylglycosides of maltose and cellobiose, both of which contain glucopyranose residues only, give formic acid at different rates. For example, methylmaltoside yields 1 mol. of formic acid in about 100 hours, whilst the cellobioside gives only 0.86 mol. in this time and 300 hours are necessary for the liberation of one equivalent of acid. This low yield of formic acid from methylcellobioside (X) could be explained by the intermediate formation of a lactol grouping such as (XI) which on further oxidation would yield not free formic acid but a formyl ester (XII). An examination of the model of the methylcellobioside molecule (and similarly of the sucrose molecule) reveals that the hydroxyl groups are so situated in space that lactol formation can readily take place, whereas the configuration of the groups in the molecule of the methylmaltoside is unfavourable for the formation of lactol groupings.

This oxidation of an intermediate lactol with formation of an ester of formic acid instead of free formic acid receives support from a study of the oxidation of mannitol. The oxidation of this hexahydroxy-alcohol yields two mols. of formaldehyde and formic acid. A quantitative

estimation of the formic acid, however, showed that the yield of this acid reached 95% of 4 mols. under the standard conditions and was not complete until the reaction had proceeded for about



400 hours. The primary oxidation of mannitol (XIII) may occur in one of five places in the molecule. It may give either (a) a pentose, (b) a tetrose, or (c) glyceraldehyde as the main reaction product. Other things being equal, reactions (a) and (b) will predominate. The pentose and tetrose which result from this oxidation may exist either as *aldehyde*-sugars or as ring structures. Should oxidation of the ring structure or lactol form occur, then a formic ester will be produced with a consequent lowering in the yield of titratable formic acid. On standing in water these esters will undergo hydrolysis and further oxidation, and a consequent slow rise in the titration figure will result. This formation of ester groupings from the oxidation of a lactol is small, since in no case have we encountered a yield of formic acid of less than 90% of the theoretical in our experiments on the oxidation of the sugar glycosides under the standardised conditions. In the oxidation of the reducing sugars, however, low yields of formic acid are produced when using our standardised reaction conditions. In certain instances, however, side reactions, with the formation of iodine, explain, in part, the low yields of formic acid produced in this complex oxidation reaction.

EXPERIMENTAL.

Oxidation with Sodium or Potassium Periodate. General Procedure.—Reactions were carried out in diffused light at 15–20° (with shaking when potassium periodate was used), in 500 c.c. stoppered bottles which had been cleaned with chromic acid and steamed out.

Sodium metaperiodate was prepared from sodium paraperiodate by recrystallisation from nitric acid. It contained no free acid since on addition of excess of ethylene glycol to its aqueous solution, sodium iodate neutral to methyl-red was formed. The ethylene glycol required was purified by distillation over solid potassium hydroxide. It was neutral to methyl-red.

The material (sufficient to give *ca.* 10 mg. of formic acid) was weighed out into a 500 c.c. stoppered bottle and dissolved or suspended in water. Excess of approximately 0.3M-sodium periodate was then added, followed by potassium chloride (5 g.) (if the oxidation was to be carried out with potassium periodate) and water to the requisite volume (usually 120 c.c.). Portions (either 10 or 20 c.c.) of the solution were withdrawn at intervals, excess of ethylene glycol was added to remove the residual periodate, and the formic acid was then determined either by titration with 0.01N-sodium hydroxide, using methyl-red as indicator, or after addition of potassium iodide by determination of the liberated iodine with 0.01N-thiosulphate. Blank experiments showed that under these conditions sodium iodate, formaldehyde, and ethylene glycol do not interfere with the estimation of formic acid and that the formic acid produced is not destroyed.

Oxidations with sodium metaperiodate. (1) α -Methylglucoside (87 mg.) was dissolved in water (115 c.c.), and sodium periodate solution (15 c.c.; 0.2M) was added. Portions of the solution (25 c.c.) were removed at intervals; ethylene glycol (approximately 0.1 c.c.) was added, and the formic acid titrated after a few minutes with 0.01N-sodium hydroxide. Titres: 6.3 c.c. (6 hours), 8.3 c.c. (22½ hours), 8.35 c.c. (47 hours), equivalent to 99.5% recovery.

After completion of oxidation a portion of the solution (50 c.c.) was extracted continuously with ether until the final extracts were neutral. The extracts were concentrated, and then required 18.8 c.c. of 0.01N-sodium hydroxide equivalent to 108% recovery of formic acid. The sodium formate obtained on evaporation of the neutralised solution gave, on heating with sulphuric acid (*d* 1.84) in a gas analysis apparatus, carbon monoxide corresponding to 99.4% of the theoretical yield of formic acid. The three different methods of determination gave reasonably concordant results, and the determination *via* carbon monoxide proves that the acid produced is formic acid.

(2) β -Methylmaltoside monohydrate (489.5 mg.) was dissolved in water (140 c.c.), and sodium periodate solution (60 c.c.; 0.275M) was added. The solution was left at 15–20°, samples (10 c.c.) were

withdrawn at intervals, ethylene glycol was added, and the solution titrated with 0.01N-barium hydroxide. At the same time the consumption of periodate and the change of optical rotation were determined.

Time (hours).	$[\alpha]_D^{19.5^\circ}$.	Formic acid produced (mols. per mol. of maltoside).	Consumption of periodate (mols. per sugar residue).
0	+176°	nil	nil
0.6	— 33	0.48	2.58
1.5	— 45	0.65	2.84
5.1	— 100	0.89	2.97
30	— 62	1.19	3.61

The reaction was not finished after 30 hours, since formic acid continued to be produced. The last figure for formic acid (1.19 mols.) is considerably more than the theoretical value (1.0 mol.). High results were obtained also with other disaccharide derivatives, and the occurrence of over-oxidation even under carefully controlled conditions rendered the use of sodium periodate unsatisfactory for quantitative work, except when the reagent was employed in very slight excess.

Oxidations with potassium metaperiodate. (3) Mannitol was oxidised to show that formaldehyde and formic acid were unaffected by the oxidation conditions used above. The mannitol (28 mg.) was dissolved in water (110 c.c.) containing sodium periodate (11 c.c.; 0.236M) to which potassium chloride (5 g.) had been added. Titration of the liberated acid after addition of excess of glycol was made at intervals on portions of the solution. Found, mols. of formic acid per mol. of sugar: 3.56 (3 hours), 3.60 (98 hours), 3.80 (145 hours), 3.80 (194 hours), 3.88 (266 hours), 3.96 (338 hours), 3.96 (580 hours). Two other experiments gave similar results.

(4) α -Methyl-*d*-glucoside (81 mg.) was dissolved in water (110 c.c.) containing potassium chloride (5 g.), and sodium periodate (10 c.c.; 0.27M) was added. At intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of methylglucoside: 0.28 (1 hour), 0.43 (5½ hours), 0.69 (23 hours), 0.90 (51 hours), 0.91 (72 hours), 0.94 (170 hours), 0.97 (220 hours), 1.04 (460 hours).

(5) α -Methyl-*d*-galactopyranoside (111 mg.) was dissolved in water (110 c.c.), and potassium chloride (5 g.) and sodium periodate (10 c.c.; 0.236M) were added. The bottle and contents were then shaken and at intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of methylgalactoside: 0.95 (67 hours), 0.99 (120 hours), 1.01 (192 hours), 1.01 (230 hours), 1.03 (500 hours).

(6) α -Methyl-*d*-mannopyranoside (82 mg.) was dissolved in water (110 c.c.) containing potassium chloride (5 g.), and sodium periodate (10 c.c.; 0.282M) was added. The bottle and contents were shaken and at intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of methylmannoside: 0.67 (68 hours), 0.85 (121 hours), 0.93 (168 hours), 0.97 (211 hours), 0.95 (289 hours), 0.96 (405 hours).

(7) β -Methyl-*l*-arabopyranoside (89 mg.) was dissolved in water (110 c.c.) containing potassium chloride (5 g.), and sodium periodate (10 c.c.; 0.236M) was added. The bottle and contents were shaken and at intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of glycoside: 0.97 (47 hours), 0.99 (91 hours), 0.99 (143 hours), 1.01 (165 hours), 1.01 (215 hours), 1.02 (281 hours), 1.04 (362 hours), 0.99 (506 hours).

(8) α -Methyl-*d*-xylopyranoside (107 mg.) was oxidised as described for the oxidation of the arabinoside. Found, mols. of formic acid per mol. of glycoside: 0.71 (47 hours), 0.89 (91 hours), 0.93 (143 hours), 0.98 (165 hours), 0.98 (215 hours), 1.00 (287 hours), 1.02 (362 hours).

(9) β -Methylmaltoside monohydrate (249.7 mg.) was dissolved in water (70 c.c.) containing potassium chloride (2.5 g.), and sodium periodate solution (30 c.c., 0.275M) was then added. The whole was placed in a stoppered bottle which was continuously shaken. At intervals samples (10 c.c.) were withdrawn, and after addition of ethylene glycol the formic acid was titrated with 0.01N-barium hydroxide using methyl-red as indicator. Found, mols. of formic acid per mol. of maltoside: 0.13 (1½ hours), 0.53 (20 hours), 0.75 (43 hours), 0.83 (66 hours), 0.92 (91 hours), 1.01 (163 hours), 1.03 (192 hours), followed by a very slow rise. One mol. of formic acid is liberated per mol. of maltoside in 150 hours.

(10) β -Methylcellobioside (106 mg.) was dissolved in water (110 c.c.) containing potassium chloride (5 g.), and sodium periodate (10 c.c., 0.28M) was added. At intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of cellobioside: 0.69 (43 hours), 0.84 (91 hours), 0.87 (144 hours), 0.88 (185 hours), 0.89 (244 hours), 0.91 (291 hours).

(11) Amygdalin (173 mg.) was oxidised as described above (cf. Courtois and Valentino, *Bull. Soc. Chim. biol.*, 1944, **26**, 469). Found, mols. of formic acid per mol. of glycoside, 1.05 (47 hours), 1.28 (91 hours), 1.53 (143 hours), 1.83 (165 hours), 1.90 (215 hours), 2.03 (287 hours), 2.08 (362 hours), 2.00 (506 hours).

(12) Sucrose (111 mg.) was dissolved in water (105 c.c.) containing potassium chloride (5 g.), and sodium periodate (15 c.c.; 0.307M) was added. At intervals samples (20 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of sucrose: 0.84 (170 hours), 0.84 (195 hours), 0.92 (267 hours), 0.91 (315 hours), 0.91 (431 hours).

(12) Zinc borneol glucuronoside (110 mg.) was dissolved in water (105 c.c.) containing potassium chloride (5 g.), and sodium periodate (5 c.c., 0.285M) was added. At intervals samples (20 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of compound: 2.34 (162 hours), 1.74 (188 hours), 1.40 (210 hours), 1.06 (307 hours). The solution became brown owing to the separation of iodine and oily droplets of bornyl formate were observable.

(13) The methyl ester of α -methylgalacturonoside (21.95 mg.) was dissolved in water (200 c.c.) containing potassium chloride (5 g.), and sodium periodate (5 c.c., 0.308M) was added. At intervals samples (20 c.c.) were withdrawn and titrated. Found, mols. of formic acid per mol. of sugar: 0.22 (3 hours), 0.79 (25 hours), 1.23 (49 hours), 1.70 (74 hours), 2.18 (117 hours), 3.74 (171 hours), 4.22 (219 hours), 4.22 (335 hours).

(14) Lactose hydrate (94 mg.) was dissolved in water (100 c.c.) containing potassium chloride (5 g.)

and sodium periodate (20 c.c., 0.2M) was added. At intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of acid per mol. of lactose hydrate : 1.85 (42 hours), 2.87 (95 hours), 3.27 (142 hours), 3.68 (185 hours), 4.13 (263 hours), 2.41 (427 hours) (iodine was liberated at this stage with a resultant fall in acid titre).

(15) Lactal (160 mg.) was dissolved in water (100 c.c.) containing potassium chloride (5 g.) and sodium periodate (20 c.c.; 0.28M) was added. At intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of acid per mol. of lactal : 0.87 (42 hours), 1.00 (95 hours), 1.09 (142 hours), 1.17 (185 hours), 1.50 (263 hours), 2.06 (427 hours).

(16) α -Methyl-*D*-mannofuranoside (106 mg.) was dissolved in water (110 c.c.) containing potassium chloride (5 g.), and sodium periodate (10 c.c.; 0.236M) was added. At intervals samples (10 c.c.) were withdrawn and titrated. Found, mols. of acid per mol. of glycoside : 1.5 (47 hours), 2.0 (91 hours) (at this stage iodine began to be liberated and the alkali titre fell), 0.43 (143 hours) (all the periodate had then been converted into iodate and iodine).

(17) Oxalic acid dihydrate (27.02 mg.) was dissolved in water (115 c.c.) containing potassium chloride (5 g.), and sodium periodate solution (5 c.c.; 0.3072M) was added. At intervals samples were withdrawn and titrated. Found, mols. of oxalic acid : 0.43 (95 hours), 0.34 (120 hours), 0.31 (144 hours), 0.18 (430 hours), 0.12 (602 hours).

The authors thank the British Cotton Industry Research Association for a Shirley Fellowship awarded to one of them (T. G. H.), and Imperial Chemical Industries Ltd. for a grant.

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[Received, November 25th, 1946.]

270. The Chloromethylation of Naphthalene and of Tetralin.

By G. M. BADGER, J. W. COOK, and G. W. CROSBIE.

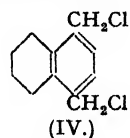
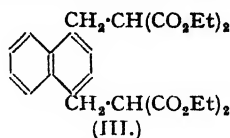
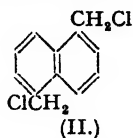
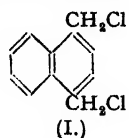
Chloromethylation of naphthalene with boiling aqueous formaldehyde and hydrochloric acid gives a mixture from which 1 : 4-bischloromethylnaphthalene and 1 : 5-bischloromethylnaphthalene have been isolated. From tetralin, 5 : 8-bischloromethyl-1 : 2 : 3 : 4-tetrahydronaphthalene has been obtained.

FROM the products of the chloromethylation of 1-chloromethylnaphthalene, Anderson and Short (*J.*, 1933, 485) obtained a crude bischloromethylnaphthalene, m. p. 130—145°, which they were unable to purify. They regarded this as being largely the 1 : 5-derivative because, on reduction, they isolated and characterised 1 : 5-dimethylnaphthalene. Furthermore, on oxidation of the crude bischloromethylnaphthalene, they obtained the corresponding 1 : 5-dicarboxylic acid. Manske and Ledingham (*Canadian J. Res.*, 1939, 17, 14) investigating the high-boiling residues resulting from Cambron's (*ibid.*, p. 10) chloromethylation of naphthalene, obtained a supposedly pure bischloromethylnaphthalene, m. p. 144°, which they regarded as the 1 : 5-derivative. Evidence for this was obtained by conversion into the dinitrile, hydrolysis to the diacetic acid, and decarboxylation to dimethylnaphthalene. The hydrocarbon was an oil, giving a picrate, m. p. 138°. As 1 : 5-dimethylnaphthalene is a solid, and as the picrates of the 1 : 5- and 1 : 4-dimethylnaphthalenes have closely similar melting points, this evidence was inconclusive.

However, supposing the major product of the bischloromethylation of naphthalene to be the 1 : 5-derivative, we decided to attempt the synthesis of *s*-hexahydropyrene by condensing bischloromethylnaphthalene with ethyl malonate, followed by hydrolysis, decarboxylation, ring-closure and reduction. While this work was in progress, two papers by Lock and Walter (*Ber.*, 1942, 75, 1158; 1944, 77, 286) became available to us, and we found that the main object of our work had already been achieved. In the second paper, these authors state that the bischloromethylnaphthalene, for which they give m. p. 150°, is not the 1 : 5- but the 1 : 4-derivative; no evidence of this was presented. Our work has confirmed this conclusion of Lock and Walter, and we have also isolated the 1 : 5-derivative from the crude bischloromethylnaphthalenes resulting from the chloromethylation both of naphthalene and of 1-chloromethylnaphthalene.

Naphthalene was chloromethylated with boiling aqueous formaldehyde and hydrochloric acid (B.P. 345,146; Lock and Walter, *loc. cit.*). Taking advantage of solubility differences in ether, the crude product was separated into several fractions, from which 1 : 5-bischloromethylnaphthalene (II), m. p. 172°, and 1 : 4-bischloromethylnaphthalene (I), m. p. 150°, were obtained by repeated recrystallisation. The constitution of each product was shown by reduction to the dimethylnaphthalene, which was characterised by the formation of the picrate and *s*-trinitrobenzene complex. The major mixed fraction resulting from the treatment with ether had m. p. 128—130°. That this contained some 1 : 5-bischloromethylnaphthalene was

shown by the isolation, in poor yield, of crystalline 1:5-dimethylnaphthalene after reduction, a result which is in agreement with the work of Anderson and Short (*loc. cit.*). However, that this fraction consisted largely of the 1:4-isomer was shown by its conversion into 1:4-bis-(ω -dicarbethoxyethyl)naphthalene (III) (Lock and Walter, *loc. cit.*). The constitution of this



product was shown by hydrolysis, followed by oxidation with potassium ferricyanide, to naphthalene-1:4-dicarboxylic acid. 1:4-Bischloromethylnaphthalene has also been converted into the corresponding dinitrile. This appears to be the same as the dinitrile described as the 1:5-derivative by Manske and Ledingham (*loc. cit.*), and we therefore believe that these authors were in error in attributing the 1:5-configuration to their products, which should all be described as 1:4-derivatives. To confirm this conclusion we have also prepared naphthalene-1:5-diacetonitrile from pure 1:5-bischloromethylnaphthalene.

The patent literature (D.R.-P. 533,850) describes the preparation of a bischloromethyl-tetralin. We have also prepared this, and have shown that it is 5:8-bischloromethyl-1:2:3:4-tetrahydronaphthalene (IV). Reduction with zinc and hydrochloric acid, or with hydrogen and palladium, gave 5:8-dimethyl-1:2:3:4-tetrahydronaphthalene, which on dehydrogenation with sulphur, or with palladised asbestos, gave 1:4-dimethylnaphthalene, characterised by the formation of the picrate and *s*-trinitrobenzene complex.

EXPERIMENTAL.

Chloromethylation of Naphthalene.—(a) A mixture of naphthalene (80 g.), aqueous formaldehyde (40%; 220 g.), and concentrated hydrochloric acid (220 g.) was boiled under reflux with vigorous stirring for 16 hours, while a current of hydrogen chloride was introduced through a tube leading to the bottom of the flask. After cooling, the aqueous layer was decanted, and the pasty mass triturated with ether (100 c.c.). In one run, this ethereal solution deposited, on standing, 1:4-bischloromethylnaphthalene (30 mg.) as colourless needles from alcohol, m. p. 149–150° (Found: C, 64.1; H, 4.5. Calc. for $C_{12}H_{10}Cl_2$: C, 64.0; H, 4.4%). This compound was later obtained pure in considerable quantity. The ethereal solution, after evaporation, gave 1-chloromethylnaphthalene (43 g.), b. p. 150–152°/13 mm., and crude bischloromethylnaphthalenes, b. p. 180–200°/13 mm., m. p. 128–130°.

The solid obtained after this ether washing was extracted with ether (200 c.c.) in a Soxhlet apparatus. The ether deposited, on cooling, crude bischloromethylnaphthalene (19 g.), m. p. 128–130°. Recrystallisation from alcohol did not raise the m. p., although later work showed that this fraction contained both the 1:4- and the 1:5-isomer. The ethereal filtrate, on evaporation, gave a further impure fraction, m. p. 105–115° (2 g.). The residue (4.0 g.), m. p. 153–159°, remaining in the Soxhlet thimble gave, after several recrystallisations from alcohol, colourless needles of 1:5-bischloromethylnaphthalene, m. p. 171.5–172.5° (Found: C, 64.0; H, 4.4. $C_{12}H_{10}Cl_2$ requires C, 64.0; H, 4.4%).

The above experiment was successfully repeated several times, but in two large scale runs naphthalene (700 g.) gave crude bischloromethylnaphthalene (300 g.) from which no pure 1:5-bischloromethylnaphthalene could be isolated by the above procedure. The crude product was soluble in ether (500 c.c.) and, after several recrystallisations, gave pure 1:4-bischloromethylnaphthalene.

(b) Crude bischloromethylnaphthalene was also obtained by chloromethylating 1-chloromethylnaphthalene (250 g.) in light petroleum (b. p. 100–120°; 300 c.c.) with paraformaldehyde (60 g.) and anhydrous zinc chloride (15 g.), by the method of Anderson and Short, except that the reaction was carried out on the steam-bath, and that hydrogen chloride was passed for 24 hours. The product, obtained in ca. 60% yield, was separated as above, and gave 1.5 g. of pure 1:5-bischloromethylnaphthalene, m. p. 171.5–172.5°.

Reduction of fraction, m. p. 128–130°. A mixture of bischloromethylnaphthalene, m. p. 128–130° (1.2 g.), in a little alcohol, and zinc dust (1.5 g.) was boiled for 1 hour, concentrated hydrochloric acid being added at intervals. After distillation (b. p. 60–65°/0.2 mm.), the product was dissolved in 50% acetone. After standing, the crystalline product which separated (75 mg.) was recrystallised from alcohol, and had m. p. 79.5–80.5°. The orange-red picrate had m. p. 138–139°, and the product isolated was therefore 1:5-dimethylnaphthalene, in agreement with Anderson and Short (*loc. cit.*).

Reduction of 1:4-bischloromethylnaphthalene. 1:4-Bischloromethylnaphthalene (m. p. 149°) was reduced in about 50% yield as above. The product formed a colourless oil, b. p. 132–134°/15 mm. (Found: C, 92.4; H, 7.4. Calc. for $C_{12}H_{12}$: C, 92.3; H, 7.7%). The picrate crystallised from methanol in long orange-red needles, m. p. 142–144° (Found: N, 10.9. Calc. for $C_{12}H_{12}O_4N_2$: N, 10.9%). Kloetzel (*J. Amer. Chem. Soc.*, 1940, **62**, 1708) gives m. p. 143–144°. The *s*-trinitrobenzene complex formed yellow needles, from methanol, m. p. 164–166° (Found: N, 11.6. Calc. for $C_{12}H_{12}O_6N_6$: N, 11.4%). Kloetzel (*loc. cit.*) gives m. p. 165–166°. The reduction product was therefore 1:4-dimethylnaphthalene.

The reduction was also carried out in almost quantitative yield by hydrogenation over palladium black in acetone.

Reduction of 1:5-bischloromethylnaphthalene. 1:5-Bischloromethylnaphthalene (m. p. 172°) was reduced as above with zinc and hydrochloric acid. The 1:5-dimethylnaphthalene, which crystallised

from the reaction mixture, was purified by sublimation at $100^{\circ}/13$ mm., and formed colourless lustrous plates, m. p. $80-81^{\circ}$ (Found : C, 92.2; H, 7.6. Calc. for $C_{15}H_{11}$: C, 92.3; H, 7.7%); Butz (*J. Amer. Chem. Soc.*, 1940, **62**, 2557) gives m. p. 80° , and Anderson and Short (*loc. cit.*) give m. p. $80-80.5^{\circ}$. The picrate formed orange-red needles, from methanol, m. p. $138-139^{\circ}$ (Found : N, 10.9. Calc. for $C_{15}H_{11}O_7N_3$: N, 10.9%); Butz (*loc. cit.*) gives m. p. 137° , and Anderson and Short (*loc. cit.*) give m. p. $138-139^{\circ}$. The *s*-trinitrobenzene complex formed yellow needles, from alcohol, m. p. $158-159^{\circ}$ (Found : N, 11.3. $C_{15}H_{11}O_9N_3$ requires N, 11.4%).

1 : 4-Bis-(ω -dicarboxyethyl)naphthalene.—Ethyl malonate (200 g.) was added to a solution of sodium (18 g.) in alcohol (300 c.c.). After cooling, bischloromethylnaphthalene, m. p. $128-130^{\circ}$ (23 g.), suspended in alcohol (200 c.c.) was added. After 10 hours' refluxing the product was worked up in the usual way. The ester (20 g.) formed colourless needles, from alcohol, m. p. $68.5-69^{\circ}$ (Found : C, 65.8; H, 6.7. Calc. for $C_{26}H_{22}O_8$: C, 66.1; H, 6.8%); Lock and Walter (*loc. cit.*) give m. p. 66.5° . A solution of this ester (20 g.) in methanol (75 c.c.), water (150 c.c.), and sodium hydroxide (36 g.) was refluxed for 8 hours, a further quantity (10 g.) of sodium hydroxide being added after the first 4 hours. The bismalonic acid (9 g.) was recrystallised from water. It decomposed at about 140° with evolution of gas, finally melting at $255-256^{\circ}$.

Proof of constitution. A solution of this acid (2 g.), potassium ferricyanide (300 g.), potassium hydroxide (43 g.), and water (1 l.) was heated at $70-80^{\circ}$, with stirring, for 24 hours. A further quantity (80 g.) of potassium ferricyanide and potassium hydroxide (14 g.) in a little water was then added, and the heating continued for 8 hours. After cooling, the filtered solution was acidified, and the precipitate collected, suspended in water, and extracted with ether. The ethereal extract on evaporation gave an acid, m. p. $309-310^{\circ}$ (75 mg.). The methyl ester had m. p. $63-64^{\circ}$. These constants are in agreement with the published figures for naphthalene-1 : 4-dicarboxylic acid.

Naphthalene-1 : 4-diacetonitrile.—The following procedure was found superior to that of Manske and Ledingham (*loc. cit.*). A mixture of 1 : 4-bischloromethylnaphthalene, m. p. $148-150^{\circ}$ (0.5 g.), potassium cyanide (0.5 g.) in a little water, and alcohol (30 c.c.) was boiled under reflux for 2 hours. After addition of water, the naphthalene-1 : 4-diacetonitrile (0.3 g.) was recrystallised from alcohol, and formed colourless prisms, m. p. $140-142^{\circ}$ (Found : C, 81.7; H, 4.75. Calc. for $C_{14}H_{10}N_2$: C, 81.55; H, 4.85%). The same compound was obtained following a similar experiment with crude bischloromethylnaphthalene, m. p. $128-130^{\circ}$. This compound is evidently identical with the derivative, m. p. 140° , described by Manske and Ledingham (*loc. cit.*) as the 1 : 5-derivative.

Naphthalene-1 : 5-diacetonitrile.—This was prepared as above, using 1 : 5-bischloromethylnaphthalene. The naphthalene-1 : 5-diacetonitrile formed colourless small needles, m. p. $188-189^{\circ}$ (Found : C, 81.4; H, 4.6. $C_{14}H_{10}N_2$ requires C, 81.55; H, 4.85%).

Chloromethylation of Tetralin.—Freshly distilled tetralin (90 g.), concentrated hydrochloric acid (210 g.), and aqueous formaldehyde (40%; 220 g.) were boiled under reflux, with stirring, for 48 hours, while hydrogen chloride was passed in. The cooled mixture was extracted with ether, and the ethereal solution dried and evaporated. The oily residue partly crystallised. The solid was collected, washed with a little ether, and recrystallised from alcohol. **5 : 8-Bischloromethyl-1 : 2 : 3 : 4-tetrahydronaphthalene** (10 g.) was obtained as colourless lustrous needles, m. p. $117-118^{\circ}$ (Found : C, 62.9; H, 6.0. $C_{12}H_{14}Cl_2$ requires C, 62.9; H, 6.1%). The oil was collected in two fractions, b. p. $150-180^{\circ}/17$ mm. (85 g.), and $180-195^{\circ}/13$ mm. (12 g.). The latter deposited a further quantity (2 g.) of bischloromethyltetralin on standing.

5 : 8-Dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. **5 : 8-Bischloromethyl-1 : 2 : 3 : 4-tetrahydronaphthalene** (4.5 g.) was reduced with zinc and hydrochloric acid, in alcohol, as described for the bischloromethylnaphthalenes. The **5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene** (0.8 g.) was obtained as a colourless oil, b. p. $125^{\circ}/14$ mm. (Found : C, 90.1; H, 10.25. Calc. for $C_{14}H_{18}$: C, 90.0; H, 10.0%) (cf. Barnett and Sanders, *J.*, 1933, 434). The reduction was also carried out, in almost quantitative yield, by hydrogenation over palladium black in acetone.

Dehydrogenation of 5 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. The above dimethyltetrahydronaphthalene (0.5 g.) was dehydrogenated with sulphur (0.3 g.) at $230-250^{\circ}$ for 2 hours. The product was converted into the picrate (0.6 g.), which formed orange-red needles, m. p. $142-143^{\circ}$, alone, or mixed with the picrate of 1 : 4-dimethylnaphthalene. The *s*-trinitrobenzene complex formed yellow needles, m. p. $163-165^{\circ}$, alone, or mixed with the *s*-trinitrobenzene complex of 1 : 4-dimethylnaphthalene. The same results were obtained when the dehydrogenation was carried out with palladised asbestos at 240° for 5 hours.

We thank Mr. J. M. L. Cameron for the microanalyses. One of us (G. M. B.) has been working with the aid of an Imperial Chemical Industries Research Fellowship.

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[Received, January 1st, 1947.]

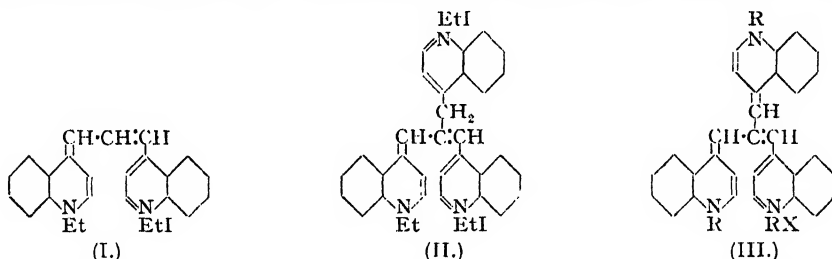
271. Some Trinuclear Cyanine Dyes. Part I. The Synthesis of Neocyanines.

By FRANCES M. HAMER, RUSSELL J. RATHBONE, and BARBARA S. WINTON.

Neocyanine is a trinuclear cyanine dye, which had been obtained as a by-product by the action of alkali on a lepidinium salt in the presence of iodoform or ethyl orthoformate, and for which three formulæ had been proposed. That which represents it as being both a substituted trimethincyanine and a substituted pentamethincyanine has now been established by synthesis. Analogous dyes having three similar heterocyclic nuclei other than 4-linked quinoline have also

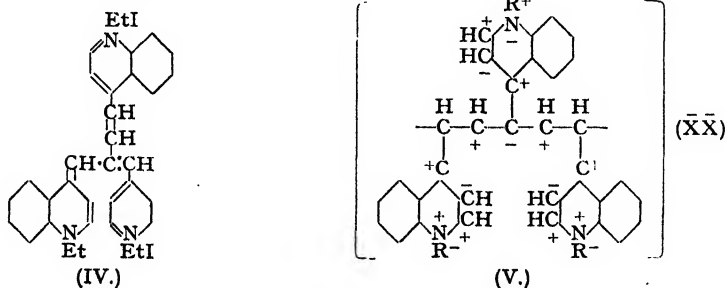
been synthesised. The necessary branched-chain intermediates, consisting of *N*-alkyldihydro-derivatives of heterocyclic bases, with a dianilisoisopropylidene group in the reactive position, were prepared from the corresponding methylene bases or their anilomethyl derivatives, by heating with ethylisoformanilide and zinc chloride. Their condensation with heterocyclic quaternary ammonium salts, having a reactive methyl group, resulted in neocyanines identical with those obtained empirically, when such existed. The absorption maxima of the trinuclear dyes have been compared with those of the related tri- and penta-methincyanines.

NEOCYANINE, a new sensitiser for the infra-red, was announced by Dundon, Schoen, and Briggs (*J. Opt. Soc. Amer.*, 1926, **12**, 397) as sensitising more powerfully beyond 8000 Å. than any dye previously reported. They said it had been isolated by H. T. Clarke as a less soluble by-product in the preparation of 4:4'-carbocyanine but did not specify his method. At that time, the normal method for preparing a 4:4'-carbocyanine, apart from the synthesis by Mills and Braunholtz which established its constitution (I) (*J.*, 1923, **123**, 2804), consisted in treating a lepidinium salt with alkali in the presence of formaldehyde or chloroform (Adams and Haller, *J. Amer. Chem. Soc.*, 1920, **42**, 2661). Only in 1928 did the acceptance of a British patent disclose that neocyanine had been produced in a 4:4'-carbocyanine preparation in which iodoform had been used instead (Kodak Ltd., B.P. 292,274/1927); the corresponding American patent did not appear for another three years (Clarke, U.S.P. 1,804,674/1931). Meanwhile one of us (Hamer, *J.*, 1927, 2796), in describing a general method for the preparation of carbocyanines by condensing a quaternary, heterocyclic ammonium salt having a reactive methyl group, with ethyl orthoformate in the presence of pyridine, recorded that the 4:4'-carbocyanine was accompanied by a by-product, identical with neocyanine. Soon afterwards, in preparing a neocyanine from each of three lepidinium salts, a modified method gave 36—41% yields. Analyses led to the conclusion that the neocyanine molecule had been formed from three molecules of lepidine alkyl halide, with elimination of hydrogen halide, and that either one or two



additional carbon atoms had entered the molecule. Based on the former supposition, the first neocyanine formula (II), showing it as a β-substituted 4:4'-carbocyanine (I), was proposed (Hamer, *J.*, 1928, 1472).

To dyes prepared from lepidinium and from quinaldinium salts, with carbon tetrachloride and alkali, Ogata and Tamura assigned formulæ such as (III) (*Bull. Inst. Phys. Chem. Res. Japan*, 1934, **13**, 475), but Ogata subsequently disclaimed these (*ibid.*, p. 491) and adopted formulæ of type (II) for dyes of the neocyanine class, which he prepared from alkiodides of several heterocyclic bases with orthoformic ester or diphenylformamidine in the presence of various condensing agents (*Proc. Imp. Acad. Tokyo*, 1932, **8**, 503; *ibid.*, 1933, **9**, 602; *Bull. Inst. Phys. Chem. Res. Japan*, 1934, **13**, 497).



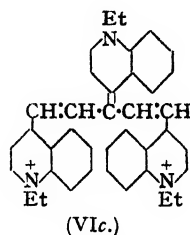
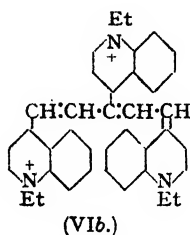
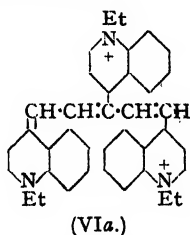
In 1931 Brooker described the neocyanines of the thiazole series and in addition to a formula of type (II) suggested an alternative (IV) with a different carbon chain (B.P. 408,273/1931).

Since alkali would be likely to convert (II) into (III), whereas (IV) had the advantage of explaining the stability of the neocyanines to alkali, formula (IV) was preferred to (II) (Brooker, Hamer, and Mees, *Phot. J.*, 1933, 57, 258; *J. Opt. Soc. Amer.*, 1933, 23, 216).

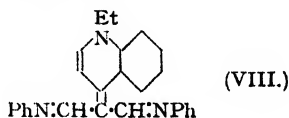
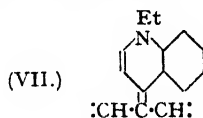
In 1935 W. König, in a theoretical paper on the chemistry of sensitizers, expressed his disbelief in formula (II) and said that he regarded neocyanine as a pentamethincyanine of formula (V). He pointed out that whereas (V) has 4:4'-linkings, other analogous substances with 2:2'-linkings are also possible, and he gave a general formula for those (*Z. wiss. Phot.*, 1935, 34, 15).

The essential feature of König's formula was the symmetrical attachment of the three heterocyclic nuclei to an unbranched-pentamethin chain, and concurrence with this view of the structure was at once expressed (Hamer, *Chem. and Ind.*, 1935, 13, 640) on the ground that it accorded with a reasonable manner of formation of the dye; neocyanine could be regarded as arising from the condensation of the methyl group of lepidine ethiodide with two molecules of ethyl orthoformate and the subsequent condensation of the resulting intermediate with two more molecules of lepidine ethiodide.

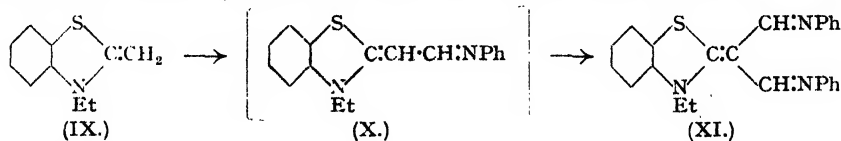
On the modern views a neocyanine kation of this structure would have its two units of positive charge distributed over the three basic groups. It cannot therefore be represented by a single structural formula, but would be regarded as a resonance hybrid of the three canonical structures (VIa, b, and c).



These formulæ, in particular (VIc), suggest the possibility of a rational synthesis of neocyanine from a suitable intermediate containing the grouping (VII), and the dianilo-compound (VIII) seemed most likely to fulfil this purpose. We have succeeded in preparing a number of dianils of this type and have found that with their aid the synthesis of the corresponding neocyanines can in fact be readily accomplished.



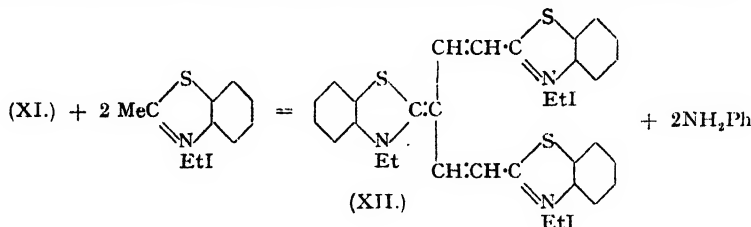
The synthesis was first carried out in the benzthiazole series, with the aid of ethylisoformanilide which, as Knott has recently shown (*J.*, 1946, 120), condenses even more readily than diphenylformamidine (I.C.I. Ltd., Piggott, and Rodd, B.P. 344,409/1929) with pyridinium salts having a reactive methyl group. As a starting point we employed, instead of a quaternary salt, the methylene base 3-ethyl-2-methylenebenzthiazoline (IX) (Hamer, Rathbone, and Winton, this vol., p. 954). Heated with ethylisoformanilide in the presence of zinc chloride, this yielded a zinc chloride complex of the base (XI), from which the base itself could be isolated



by appropriate treatment with alkali. The presumed intermediate (X) had already been described by Brooker and White, who obtained it by the action of alkali on 2-β-anilino vinyl-benzthiazole ethiodide (U.S.P. 2,298,732/1942), and we found that it also could be condensed with ethylisoformanilide to yield (XI). It is safe to assume that the methin group attached to the ring is attacked, rather than the more remote methin group, since the former is in the well-known reactive position. We should have liked to have obtained direct proof of this assumption and therefore prepared the α- and β-methyl derivatives of (X) (Hamer, Rathbone,

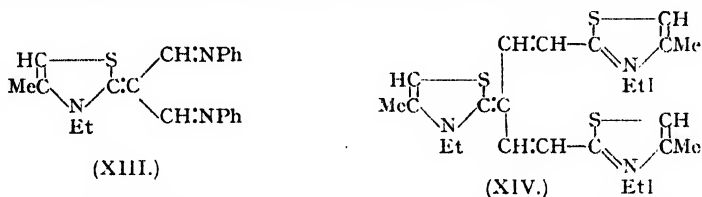
and Winton, *loc. cit.*), hoping to be able to condense the β -methyl derivative with ethylisoformanilide, but the attempt, as also that with the α -methyl derivative, was unsuccessful.

The final stage in the synthesis was readily effected. The dianilo-base (XI), heated for a few minutes with 2-methylbenzthiazole ethiodide, either in pyridine solution or with sodium acetate and acetic anhydride, gave in excellent yield a neocyanine (XII), identical with that obtained by Ogata's method (*Proc. Imp. Acad. Tokyo*, 1933, 9, 602; *Bull. Inst. Phys. Chem. Res. Japan*, 1934, 13, 497) from a 2-methylbenzthiazolium salt and ethyl orthoformate.



In the thiazole series we prepared the *dianilo-base* (XIII) from 4-methyl-3-ethyl-2-anilo-ethylidene- Δ^4 -thiazoline, condensed it with 2 : 4-dimethylthiazole etho-*p*-toluenesulphonate in pyridine, and isolated the dye as iodide (XIV), which was identical with that obtained by the empirical method from the same quaternary salt with ethyl orthoformate and pyridine (B.P. 408,273/1931).

Neocyanine itself was synthesised in a similar manner. The necessary *dianil* (VIII) was prepared by condensation of the methylene base from lepidine etho-*p*-toluenesulphonate with ethylisoformanilide and this, heated with lepidine ethiodide, acetic anhydride and sodium acetate,

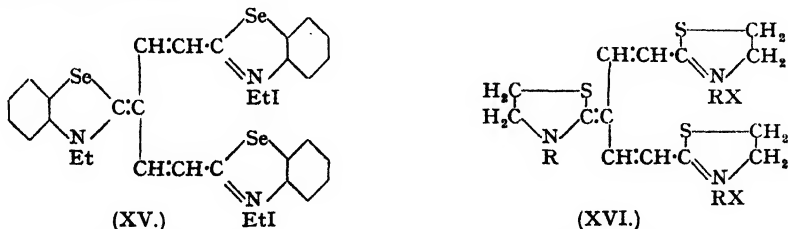


gave in 20% yield a product identical with the neocyanine obtained from lepidine ethiodide and ethyl orthoformate in the presence of pyridine (Hamer, *J.*, 1927, 2796; cf. *idem*, *J.*, 1928, 1472).

The synthesis of neocyanines in this manner may be taken as proof of the correctness of the structure now assigned to them.

In addition to the three dianilo-bases, (VIII), (XI), and (XIII), the following representatives of this class have been prepared: 5-chloro-3-ethyl-2-dianiloisopropylidenbenzthiazoline, 3-ethyl-2-dianiloisopropylidene-6 : 7-benzbenzthiazoline, 3-ethyl-2-dianiloisopropylidenbenzselanazoline, 3-methyl-2-dianiloisopropylidenethiazolidine, 3-ethyl-2-dianiloisopropylidenethiazolidine, 1-ethyl-2-dianiloisopropylidene-1 : 2-dihydroquinoline, 3-ethyl-2-dianiloisopropylidenbenzoxazoline.

From the dianils, new neocyanines were prepared, namely the *dichloride* corresponding with the di-iodide (XII), *analogues* of (XII) having, respectively, three 6 : 7-benzbenzthiazole and three 5-chlorobenzthiazole nuclei, its *seleno-analogue* (XV), and two Δ^2 -thiazoline analogues (XVI). It will naturally be understood that each of these formulæ is to be taken as the representative of a set of resonating structures.



The absorption curves of methyl-alcoholic solutions of the trinuclear dyes were plotted. They were well-defined and rather narrow, with sometimes an inflexion on the short wave-length side. Since the neocyanines might be regarded as combining the structural characters of the

tri- and penta-methincyanines, we give in the following table the wave-lengths of the absorption maxima of seven neocyanines and for comparison those of the corresponding tri- and penta-methincyanines. Certain abbreviations, obvious in conjunction with the text, have been used. Each previously recorded absorption maximum is marked with a bibliographic reference, the unmarked ones being those of compounds described in the present paper. Some of the parent cyanines were prepared for the sake of this comparison. With each of the seven neocyanines, the absorption maximum lies between that of the unsubstituted trimethincyanine and pentamethincyanine, as recorded already for one such dye (Hamer, *Chem. and Ind.*, 1935, 13, 640). The bathochromic shifts on passing from trimethincyanine to neocyanine vary from 375 to 710 Å. and those on passing from neocyanine to pentamethincyanine vary from 350 to 520 Å. Other comparisons may also be made. For instance, replacement of the three 4-linked quinoline nuclei of neocyanine by three benzthiazole nuclei caused a hypsochromic shift of 1735 Å. Replacement of three benzthiazole nuclei by three methylthiazole nuclei caused a hypsochromic shift of 140 Å., whilst their replacement by three 5-chlorobenzthiazole, three 6:7-benzbenzthiazole, or three benzselenazole nuclei caused bathochromic shifts of 90, 335, and 185 Å., respectively.

The new dyes comprised photographic sensitisers and desensitisers.

Neocyanine.	Abs. max., Å.	Trimethin- cyanine.	Abs. max., Å.	Pentamethin- cyanine.	Abs. max., Å.	Bathochromic shifts : trimethin- to neo- cyanine.	neo- to pentamethin- cyanine.
4-q } 4-q } (VI) 4-q }	7750 *	4-q } 4-q } (I)	7040 †	4-q } 4-q }	8100 †	710	350
bzth } bzth } (XII) bzth }	6015	bzth } bzth }	5570 †	bzth } bzth }	6500 †	445	485
bzbzth } bzbzth } bzbzth }	6350	bzbzth } bzbzth }	5930 †	bzbzth } bzbzth }	6870 †	420	520
Clbzth } Clbzth } Clbzth }	6105	Clbzth } Clbzth }	5625 ‡	Clbzth } Clbzth }	6560	480	455
bzSe } bzSe } (XV) bzSe }	6200	bzSe } bzSe }	5700 †	bzSe } bzSe }	6600 †	500	400
Me-th } Me-th } (XIV) Me-th }	5875	Me-th } Me-th }	5520 §	Me-th } Me-th }	6370	375	495
thiazoline } thiazoline } thiazoline }	5060	thiazoline } thiazoline }	4435	thiazoline } thiazoline }	5450	625	390

(XVI; R = Et,
X = ClO₄)

* Hamer, *Chem. and Ind.*, 1935, 13, 640.

† Fisher and Hamer, *Proc. Roy. Soc.*, 1936, A, 154, 703.

‡ Hamer, Rathbone, and Winton, this vol., p. 954.

§ Cf. Fisher and Hamer, *J.*, 1930, 2502.

|| Brooker, *J. Amer. Chem. Soc.*, 1936, 58, 662.

Nomenclature.—Some years ago we first adopted the practice of publishing the systematic names for the cyanines in addition to other names (Fisher and Hamer, *J.*, 1937, 907) or, as the structures became more complex, exclusively (Beilenson and Hamer, *J.*, 1942, 98). Thus whilst (I) may be described as 1:1'-diethyl-4:4'-carbocyanine iodide (Mills and Braunholtz, *J.*, 1923, 123, 2804), its systematic name is [bis-4-(1-ethylquinoline)]trimethincyanine iodide. This nomenclature presupposes only a knowledge of the fundamental structure of a cyanine dye; each ring is denoted by its usual description and numbering, and the positions of linking are indicated. In extending the systematic nomenclature to the present trinuclear cyanines, it is apparent that neocyanine itself might be named either as a substituted trimethincyanine or as a substituted pentamethincyanine. In introducing one fresh convention, that a trinuclear dye is named as a derivative of that parent cyanine having the shorter chain, of course we do not intend to imply that it actually is a derivative of that cyanine rather than of the one having the longer chain. A second parenthesis is introduced to comprise the third nucleus and here the numbers which indicate the position of linking and the positions of substituents are each

followed by a dash, whilst the Greek letters show the positions of attachment of the chain linking the third nucleus. Thus neocyanine is called [bis-4-(1-ethylquinoline)][$\alpha\beta'$ -dimethin-4'-(1'-ethylquinoline)]trimethincyanine di-iodide.

EXPERIMENTAL.

3-Ethyl-2-dianiloisopropylidenebenzthiazoline (XI).—3-Ethyl-2-methylenebenzthiazoline (33.17 g.; 1 mol.), zinc chloride powder (76.5 g.; 3 mols.), and ethylisoformanilide (277 c.c.; 10 mols.) were heated together at 175–180° for 2½ hours, with mechanical stirring. Acetone (700 c.c.) was added, and the mixture heated until all lumps had gone. After cooling, the zinc chloride complex was filtered off and washed with acetone. It was ground with, and stirred into, water (750 c.c.). It was filtered off, washed with methyl alcohol, boiled out twice with that solvent (1000 c.c., 200 c.c.), and washed twice with hot methyl alcohol (50 c.c. \times 2).

For converting the complex (54.2 g.) into base, it was ground with water (10 c.c. per g.) and with 40% sodium hydroxide solution (20 c.c. per g.) and the suspension was shaken with acetone (100 c.c. per g.). The acetone extract was filtered and the aqueous residue was further extracted twice with acetone (10 c.c. per g. \times 2). The extracts were dried over stick sodium hydroxide for a period of days, then filtered, and the acetone was distilled off under a vacuum (in six lots) and the concentrate (volume about 15 c.c. \times 6) cooled. The base crystallised and was filtered off and washed with methyl alcohol until the washings were no longer brown. The yield was 28% (19.76 g.). In recrystallising from methyl alcohol (110 c.c. per g.), the time of heating was kept to a minimum and the yield was 21% (15.36 g.). (After drying in a vacuum desiccator, it was analysed by the method of Carius, which method was used throughout this work for sulphur and halogen determinations.) (Found: S, 7.9. Calculated for $C_{24}H_{21}N_3S$: S, 8.35%). The yellow crystals had m. p. 127°, becoming orange at about 110°. The broad absorption curve had its maximum at 4020 Å. and an inflexion at 3500 Å. The base was photographically inert.

In the second method of preparation, 3-ethyl-2-aniloethylidenebenzthiazoline (X) (47 g.; 1 mol.), zinc chloride (94 g.; 4.1 mols.), and ethylisoformanilide (250 g.; 10 mols.) were heated together at 160–185° for 1 hour. After partial cooling, acetone (1000 c.c.) was added; refluxing was applied, in order to break up a hard lump. When cold, the solid was filtered off, washed with acetone, and ground with water (107 g. obtained). It was thrice boiled out with methyl alcohol (2350 c.c. \times 3) (8.01 g., 0.09 g., and 0.16 g., respectively, crystallised from the filtrates). When a test portion of the solid from the first boiling out was heated with a 2-methylbenzthiazolium salt in pyridine, it gave a red colour, whilst a test portion of the second or third, when similarly treated, gave a blue. The boiling out with methyl alcohol halved the weight of zinc chloride complex. It was converted into free base as before and gave a 17% yield (11 g.), and after recrystallisation from methyl alcohol 10% (6.46 g.). Its m. p. was the same as that of the sample prepared by the first method, and that of the mixture was identical.

5-Chloro-3-ethyl-2-dianiloisopropylidenebenzthiazoline.—5-Chloro-3-ethyl-2-methylenebenzthiazoline (24 g.; 1 mol.), zinc chloride (47 g.; 3 mols.), and ethylisoformanilide (170 g.; 10 mols.) were heated together at 190°, with mechanical stirring, for 1½ hours. After partial cooling, acetone (1000 c.c.) was added and the solid was filtered off, ground with water (28 g. left), and boiled out with methyl alcohol (500 c.c. \times 4). The filtrates varied from purple to pale pink, but a negligible amount of solid (total, 0.1 g.) separated from them. The yellow zinc chloride complex (24.12 g.) was ground with 40% sodium hydroxide solution (400 c.c.) and water (200 c.c.) and extracted with acetone (5000 c.c.). The extract was dried with stick sodium hydroxide, the solvent distilled off under a vacuum, and the concentrate cooled, giving a 16% yield of crude base (7.83 g.). A sample was recrystallised from pyridine (5 c.c. per g.; yield 12%) (Found, after drying in a vacuum at 60–80°, which method of drying was employed throughout this work except where otherwise stated: Cl, 8.7. Calculated for $C_{24}H_{20}N_3ClS$: Cl, 8.5%). The yellow crystals had m. p. 182–184°. The absorption curve had its maximum at 4100 Å. and tailed off very gradually on the short wave-length side. Towards a gelatino-chloride photographic emulsion the substance exerted slight sensitisation as far as 4700 Å.

3-Ethyl-2-dianiloisopropylidene-6:7-benzbenzthiazoline.—To 3-ethyl-2-methylene-6:7-benzbenzthiazoline (11.43 g.) was added ethylisoformanilide; zinc chloride powder was stirred in, and the mixture heated. It was stirred by hand, in order to break up the lumps of zinc chloride, until the oil-bath temperature reached 80°. Mechanical stirring was then applied and the temperature was raised to 175–180° and held there for an hour. After cooling, the hard reaction product was treated with acetone (250 c.c.), being heated and stirred at intervals for a few hours in order to break up the lumps. The solid was filtered off, washed with acetone, ground with water, and then boiled out four times with methyl alcohol (450 c.c. \times 4). The residual complex (9.52 g.) was ground with water (10 c.c. per g.), added to acetone (100 c.c. per g.), and shaken with 40% sodium hydroxide solution (20 c.c. per g.) until all solid had disappeared. The acetone layer was filtered, and the aqueous part further twice extracted with acetone (200 c.c., 100 c.c.). The extracts were dried over stick sodium hydroxide for 2 days. The filtrate was then concentrated under a vacuum until almost all the acetone had been removed and only a little aqueous liquid was left. The solid which separated on cooling was filtered off and obtained, after washing with acetone, in 21% yield (4.49 g.). It was recrystallised from methyl alcohol (4000 c.c.), the time of heating being reduced to the very minimum. The yield was 9% (1.86 g.) but in a recrystallisation where boiling with mechanical stirring went on for 7 minutes the yield was only half that (Found: S, 7.2. Calculated for $C_{28}H_{23}N_3S$: S, 7.4%). The dull yellow crystals melted at about 173° with previous darkening and shrinking. The absorption maximum was at 3890 Å. and the base did not sensitise a gelatino-chloride photographic emulsion.

3-Ethyl-2-dianiloisopropylidenebenzselazoline.—3-Ethyl-2-aniloethylidenebenzselazoline (20 g.; 1 mol.), ethylisoformanilide (44 g.; 5 mols.), and zinc chloride (18 g.; 2.2 mols.) were heated together at 160–170° for 30 minutes. The product was treated with water, and the solid was next thoroughly ground and washed with acetone and boiled out with methyl alcohol (1400 c.c.). The zinc chloride

complex (11.5 g.) was converted into base, by grinding to a paste with water and shaking with 40% sodium hydroxide solution (100 c.c.) and acetone (500 c.c.). The filtered acetone extract was dried with stick sodium hydroxide, then concentrated considerably. The base was filtered off, washed with spirit, and obtained in 14% yield (3.8 g.). On recrystallisation from methyl alcohol (80 c.c. per g.), the yield fell to 7% (Found : N, 9.9. $C_{24}H_{21}N_3Se$ requires N, 9.75%). The bright yellow crystals had m. p. 140° (decomp.). The absorption curve had a maximum at 4070 Å. and an inflexion at 3550 Å. The substance did not sensitise a gelatino-chloride photographic emulsion.

In a second method of preparation, 3-ethyl-2-methylenebenzelenazoline (22.4 g.; 1 mol.), ethylisoformanilide (75 c.c.; 5 mols.) and zinc chloride (41 g.; 3 mols.) were heated together at 150–170° for 2 hours. The washed product was boiled out with methyl alcohol (1000 c.c.), leaving a residue of zinc chloride complex (5.62 g.). The yield of crude base was 10%, falling to 7% on recrystallisation from methyl alcohol. M. p. and mixed m. p. showed its identity with the sample prepared by the first method. A by-product (5.25 g.) which separated from the methyl-alcoholic extract of crude zinc chloride complex was identified as follows as a zinc chloride complex of 3-ethyl-2-aniloethylidenbenzelenazoline. It was treated with 40% sodium hydroxide solution (40 c.c.) and acetone (100 c.c.); on pouring the concentrated acetone extract into water, a base (4.11 g.) resulted, and after recrystallisation from light petroleum (b. p. 80–100°), consisted of a 20% yield (2.83 g.) of what was proved to be 3-ethyl-2-aniloethylidenbenzelenazoline, by comparison with a genuine specimen.

It is noteworthy that we were unable to prepare the dianilo-base by the action of ethylisoformanilide and zinc chloride on the zinc chloride complex of 3-ethyl-2-aniloethylidenbenzelenazoline, which tallies with the fact that it could not be thus prepared from the hydrochloride either, *i.e.*, from 2-β-anilinoethylidenbenzelenazole ethochloride.

4-Methyl-3-ethyl-2-dianiloisopropylidene-Δ⁴-thiazoline (XIII).—4-Methyl-3-ethyl-2-aniloethyliden-Δ⁴-thiazoline (48.8 g.; 1 mol.), ethylisoformanilide (152 g.; 5 mols.), and zinc chloride (80 g.; 3 mols.) were heated together at 150–170° for 2 hours. The crude zinc chloride complex was washed with acetone, treated with water, and boiled out with methyl alcohol (3200 c.c.) (64.8 g. left). It was then shaken vigorously at room temperature with 40% sodium hydroxide solution (560 c.c.) and acetone (3200 c.c.). The acetone extract was concentrated to small bulk and the base precipitated by addition of ice-water (31.6 g. obtained). On recrystallisation from light petroleum (b. p. 80–100°; 35 c.c. per g.), a 35% yield (23.9 g.) of golden-yellow crystals was obtained (Found : S, 9.05. $C_{21}H_{21}N_3S$ requires S, 9.25%). M. p. 111° (decomp.). The absorption maximum was at 3475 Å. The base was inert towards a gelatino-chloride photographic emulsion.

3-Methyl-2-dianiloisopropylidenethiazolidine.—3-Methyl-2-aniloethylidenethiazolidine (10.20 g.; 1 mol.), ethylisoformanilide (70 c.c.; 10 mols.), and zinc chloride (19.13 g.; 3 mols.) were heated together at 175–180° for 1½ hours. The warm viscous mass was treated with acetone (150 c.c.). The solid was filtered off, treated with water (300 c.c.), and boiled out four times with methyl alcohol (125 c.c. × 4) (12.85 g. of zinc chloride complex left).

In order to liberate the free base, the zinc chloride complex (8 g.) was ground with acetone (120 c.c.), and the mixture cooled with ice and stirred mechanically. An ice-cold solution of sodium (2 g.) in absolute alcohol (120 c.c.) was run in, and stirring with cooling was applied for 10 minutes; when the sodium ethoxide solution was first added, the liquid became bright yellow. The solid, which apparently consisted of zinc oxide and sodium zincate, was filtered off and washed with acetone (16 c.c.). On pouring the filtrate and washings into ice-cold water (500 c.c.), the base was precipitated as a yellow solid, being obtained in 36% yield (3.33 g.). Rapid recrystallisation from methyl alcohol (25 c.c. per g.) gave a 30% yield, but when boiling and mechanical stirring were applied for 5 minutes, decomposition took place, so that the yield was only 4% (Found : S, 9.95. $C_{19}H_{19}N_3S$ requires S, 10.0%). Recrystallisation from light petroleum (b. p. 80–100°) was less precarious and gave an 18% yield. The lemon-yellow crystals had m. p. 127°. The absorption maximum was at 3720 Å. The base was photographically inert.

3-Ethyl-2-dianiloisopropylidenethiazolidine.—The zinc chloride complex (66 g.) was prepared similarly from 3-ethyl-2-aniloethylidenethiazolidine (90.6 g.) and was converted (in 20 g. lots) into the free base, of which the yield was 33% (43 g.). After recrystallisation from light petroleum (b. p. 80–100°; 120 c.c. per g.), the yield was 22% (Found, after drying in a vacuum at 50° : S, 9.6. $C_{20}H_{21}N_3S$ requires S, 9.55%). The bright yellow crystals had m. p. 104°. The absorption maximum of the broad curve was at 3530 Å. The base was photographically inert in a gelatino-chloride emulsion.

1-Ethyl-4-dianiloisopropylidene-1 : 4-dihydroquinoline (VIII).—1-Ethyl-4-methylene-1 : 4-dihydroquinoline (10.44 g.; 1 mol.) was treated with ethylisoformanilide (90.5 c.c.; 10 mols.) and zinc chloride powder (25 g.; 3 mols.) and the mixture was heated in an oil-bath and stirred by hand until the temperature reached 80° and the large lumps had been broken up. Mechanical stirring was then applied and the mixture was heated at 175–185° for 1½ hours. Whilst still warm, the reaction mixture was treated with acetone (150 c.c.), whereupon hardening occurred. After intermittent heating, the dark syrupy liquid was poured off and the hard residue heated with another equal amount of acetone, and finally with yet another, which left no residue. All the dark mixtures were filtered after cooling and the residual solid was further washed with acetone, and with water (600 c.c.). The solid was boiled out thrice with methyl alcohol (400 c.c. × 3). The first filtrate was almost black, the second dark brown, the third amber, and the residual solid (12.74 g.) a clean, bright orange.

In order to obtain the base, the zinc chloride complex (2 g.) was ground with acetone (30 c.c.), and the suspension cooled with ice and treated with an ice-cold solution of sodium (0.45 g.) in absolute alcohol (30 c.c.). The solid was crushed until orange streaks were no longer visible : the liquid became dark yellow. The grey residue was filtered off and washed with a cooled alcohol-acetone mixture : the filtrates were poured into ice-cold water (60 c.c.). Before the bright yellow solid could be filtered off it had become brown. It was washed with ice-cold water and dried in the air and finally in a vacuum desiccator. The yield of base was 34% (1.24 g.). 1 G. was twice extracted with hot light petroleum (b. p. 40–60°; 20 c.c. × 2), each extract being filtered into a tube cooled with ice. The yield of recrystallised product was only 3% (Found, after drying in a vacuum desiccator : N, 11.0. $C_{24}H_{21}N_3$

requires N, 11.15%). When heated, the light brown powder began to shrink at 90°; decomposition was gradual and the substance was quite black by 154° but without any definite m. p. The absorption maximum was at 4785 Å., with another maximum at 4020. The base sensitised a gelatino-chloride photographic emulsion weakly up to 5400 Å., with the maximum at 4950.

1-Ethyl-2-dianiloisopropylidene-1 : 2-dihydroquinoline.—1-Ethyl-2-methylene-1 : 2-dihydroquinoline (10.14 g.) was heated with ethylisoformanilide and zinc chloride as in the previous preparation. The warm product was treated with acetone (120 c.c.) and left to stand, with occasional warming. The suspension was poured off from the hard residue, which was similarly treated with a second portion of acetone (120 c.c.) and later with a third (120 c.c.). After cooling, the extracts were filtered, giving a black, treacly filtrate. The residual product was washed with acetone, ground with water (400 c.c.), and thrice boiled out with methyl alcohol (750 c.c. \times 3). The residue of zinc chloride complex was a dull orange (7.31 g. obtained).

Its conversion into base was carried out as in the preceding preparation. The yield of washed, dried base was 7% (0.82 g. from two 2 g. lots of complex). It was a dirty yellow when first precipitated but finally a dark green. On recrystallising as quickly as possible from light petroleum (b. p. 80–100°; 60 c.c. per g.), the yield dropped to 1% (Found, after drying in a vacuum desiccator: N, 10.85. $C_{24}H_{21}N_3$ requires N, 11.15%). The light brown powder had no definite m. p.; shrinking began at about 95° and considerable decomposition had occurred by 105°. The broad absorption curve had its maximum at 4100 Å. On a gelatino-chloride emulsion the base conferred traces of sensitivity up to 5200 Å.

3-Ethyl-2-dianiloisopropylidenebenzoxazoline.—3-Ethyl-2-aniloethylidenebenzoxazoline (106 g.; 1 mol.), ethylisoformanilide (300 c.c.; 5 mols.) and zinc chloride (168 g.; 3 mols.) were heated together at 150–160° for 1 hour. The reaction mixture was heated with acetone, and the solid boiled out with methyl alcohol (1600 c.c.). The resultant zinc chloride complex (45 g.) was warmed and shaken with 20% sodium hydroxide solution (7.5 c.c. per g.) and acetone (65 c.c. per g.). After concentration, the acetone extract was precipitated with aqueous ammonium chloride solution, and the crude base recrystallised from methyl alcohol (100 c.c. per g.) (18 g. obtained). As a sample left some ash on heating, the base was purified by suspending it in spirit (20 c.c. per g.) and acidifying with concentrated hydrochloric acid (4 c.c. per g.). The filtered solution was treated with ammonia and the precipitated base was obtained in 6% yield (8.6 g.). On recrystallisation from methyl alcohol (700 c.c.), the yield dropped to 4% (5.3 g.) and on a second recrystallisation (from 450 c.c.) to 3% (Found: N, 11.6. $C_{24}H_{21}ON_3$ requires N, 11.45%). The bright yellow crystals had m. p. 210° (decomp.). The absorption maximum was at 3755 Å. The compound was photographically inert.

[Bis-2-(3-ethylbenzthiazole)][aβ'-dimethin-2'-(3'-ethylbenzthiazole)]trimethincyanine Di-iodide (XII).—3-Ethyl-2-dianiloisopropylidenebenzthiazoline (XI) (0.19 g.; 1 mol.) was ground with 2-methylbenzthiazole ethiodide (0.31 g.; 2 mols.) and the mixture heated with pyridine (2 c.c.) at 130–140° for 5 minutes. A blue colour rapidly developed and solid crystallised. It was filtered off when cold and washed with pyridine and with ether, being obtained in 90% yield (0.36 g.). After recrystallisation from methyl alcohol (100 c.c. per g.) it was obtained in 74% yield (0.28 g.) (Found: I, 31.55. $C_{32}H_{31}N_5S_3$ requires I, 31.45%). The dark green crystals had m. p. 243° (decomp.). The absorption maximum was at 6015 Å. with an inflexion to the curve at 5550. The dye caused weak photographic sensitisation, extending to 7000, with its maximum at 6450 Å.

In a preparation in which the pyridine was replaced by anhydrous sodium acetate (0.33 g.; 8 mols.) and acetic anhydride (2 c.c.), the yield of crude product, after washing with acetic anhydride, ether, and water, was 65%, and after recrystallisation from methyl alcohol it was 55%.

Ogata (*Bull. Inst. Phys. Chem. Res. Japan*, 1934, 13, 497; cf. *idem*, *Proc. Imp. Acad. Tokyo*, 1933, 9, 602) heated together 2-methylbenzthiazole ethiodide, orthoformic ester, and succinic acid at 170°, and claimed a 15% yield of thiocarbocyanine and a 1% yield of more soluble neocyanine, with no indication that a troublesome purification is necessary. In repeating the preparation, our best result was obtained by heating together 2-methylbenzthiazole etho *p*-toluenesulphonate (3 g.; 3 mols.), succinic acid (2.72 g.; 8 mols.), and ethyl orthoformate (3 c.c.; 3.2 mols.) at 180–190° for 10 minutes. After cooling, the liquid was poured off, and the residual tar washed with absolute ether (25 c.c.). It was then heated with a solution of crystalline sodium carbonate (6.6 g.; 8 mols.) in water (10 c.c.), so as to remove any succinic acid. To convert the dyes into iodides, potassium iodide (3 g.) was added and the green solid was filtered off. In addition to a dye giving a pink and one giving a blue solution, other matter was present. After two washings with water (10 c.c. \times 2), the residue (1.18 g.) was thrice boiled out with methyl alcohol (10 c.c. \times 3). The blue dyes from the first two fractions were put together (0.33 + 0.13 g.), but the bluish-pink dye (0.10 g.) from the third was rejected. The residue was recrystallised from absolute alcohol (50 c.c.) and gave the pink thiocarbocyanine (0.20 g.). On precipitating the combined methyl-alcoholic filtrates with absolute ether (150 c.c.), a further yield of the blue dye was obtained (0.06 g., making the total 0.52 g.). The dye giving a blue solution was twice boiled out with absolute alcohol (50 c.c. per g. \times 2), and was then recrystallised from methyl alcohol (50 c.c. per g.), in which the neocyanine was considerably more soluble than in absolute alcohol. The final yield of purified thiocarbocyanine was 17% (0.15 g.) and of purified neocyanine 9% (0.09 g.) (Found: I, 31.9. $C_{32}H_{31}N_5S_3$ requires I, 31.45%). Ogata correlated his nitrogen determination with the formula $C_{31}H_{31}N_5S_3$ and gave m. p. 256° (decomp.). The present specimen was found to have the same m. p., mixed m. p., and absorption as the synthetic one.

[Bis-2-(3-ethylbenzthiazole)][aβ'-dimethin-2'-(3'-ethylbenzthiazole)]trimethincyanine Dichloride.—The preceding di-iodide (0.88 g.) was converted into the dichloride by boiling its solution in spirit (176 c.c.) with freshly precipitated silver chloride and taking the filtered solution down to dryness. The dichloride (0.52 g.; 76% yield) was given two recrystallisations from ethyl alcohol (3 c.c. per g.) and ethyl acetate (18 c.c. per g.) and thus obtained in 49% yield (Found: Cl, 10.6; S, 14.4. $C_{32}H_{31}N_5Cl_2S_3$ requires Cl, 10.4; S, 14.35%). Its green crystals melted at about 200° (decomp.). It was insoluble in anhydrous ether or in ethyl acetate but readily soluble in methyl or ethyl alcohol and in water.

[Bis-2-(3-ethyl-6 : 7-benzbenzthiazole)][aβ'-dimethin-2'-(3'-ethyl-6' : 7'-benzbenzthiazole)]trimethincyanine Di-iodide.—3-Ethyl-2-dianiloisopropylidene-6 : 7-benzbenzthiazoline (0.87 g.; 1 mol.) and 2-methyl-6 : 7-

benzbenzthiazole ethiodide (1.42 g.; 2 mols.) were ground together, treated with pyridine (16 c.c.), and heated with mechanical stirring at 130–140° for 10 minutes. The washed solid was recrystallised from methyl alcohol (600 c.c.) and gave a 56% yield (1.07 g.). A second recrystallisation from spirit (630 c.c. per g.) gave a 36% yield. Filtration of the recrystallised dye was extraordinarily slow (Found: I, 26.2. $C_{44}H_{31}N_3I_2S_2$ requires I, 26.5%). The dark bronze substance had m. p. 216° (decomp.). The absorption maximum was at 6350 Å. with an inflexion to the curve at 5900 Å. The dye did not sensitise but caused some depression of the normal sensitivity of the plate.

[Bis-2-(5-chloro-3-ethylbenzthiazole)][$\alpha\beta'$ -dimethin-2'-(5'-chloro-3'-ethylbenzthiazole)]trimethincyanine Di-iodide. — 5-Chloro-3-ethyl-2-dianiloisopropylidenebenzthiazoline (1.56 g.; 1 mol.), 5-chloro-2-methylbenzthiazole ethiodide (2.55 g.; 2 mols.), anhydrous sodium acetate (1.23 g.; 4 mols.), and acetic anhydride (10 c.c.) were heated together at 150° for 10 minutes. The washed dye (2.93 g.; 86% yield) was recrystallised from methyl alcohol (320 c.c. per g.), after which the yield was 51% (Found: 3 Cl + 2I, 39.35. $C_{32}H_{28}N_3Cl_3I_2S_2$ requires 3Cl + 2I, 39.55%). The green crystals had m. p. 240° (decomp.). The absorption maximum was at 6105 Å. with an inflexion to the curve at 5700 Å. The compound did not sensitise and strongly depressed the blue sensitivity of a photographic emulsion. A pure product was not obtained in earlier experiments where the condensing agent was pyridine.

[Bis-2-(3-ethylbenzelenazole)][$\alpha\beta'$ -dimethin-2'-(3'-ethylbenzelenazole)]trimethincyanine Di-iodide (XV). — 3-Ethyl-2-dianiloisopropylidenebenzelenazoline (0.66 g.; 1 mol.), 2-methylbenzelenazole ethiodide (1.06 g.; 2 mols.), and pyridine (6 c.c.) were heated and stirred together at 135–140° for 5 minutes. On recrystallising the washed dye (0.93 g. obtained; 65% yield) from methyl alcohol (195 c.c. per g.), the yield was 56% (0.80 g.) (Found: I, 26.85. $C_{32}H_{31}N_3I_2Se_2$ requires I, 26.75%). The dull green crystals had m. p. 226° (decomp.). The absorption maximum was at 6200 Å., with an inflexion to the curve at about 5740 Å. The compound had a strong desensitising effect on a photographic plate.

[Bis-2-(4-methyl-3-ethylthiazole)][$\alpha\beta'$ -dimethin-2'-(4'-methyl-3'-ethylthiazole)]trimethincyanine Di-iodide (XIV). — 4-Methyl-3-ethyl-2-dianiloisopropylidene- Δ^4 -thiazoline (XIII) (0.69 g.; 1 mol.), 2:4-dimethylthiazole etho-*p*-toluenesulphonate (1.25 g.; 2 mols.), and pyridine (5 c.c.) were heated together at 130° for 40 minutes. The pyridine was removed under reduced pressure, and the residue dissolved in hot spirit and poured into a hot aqueous solution of potassium iodide (2.2 g.; 8 mols.). The dye (1.04 g.; 74% yield) was recrystallised from absolute alcohol (20 c.c.) and thus obtained in 59% yield (0.82 g.) as dark blue crystals (Found: I, 36.25. Calc. for $C_{22}H_{31}N_3I_2S_2$: I, 36.3%; it had m. p. 206° (decomp.), which was also the m. p. of the mixture of this synthetic specimen with that of the one prepared by the empirical method given below. The substance had a narrow absorption curve with its maximum at 5875 Å. It sensitised to 7100 Å., the maximum lying at 6300. In these respects it was identical with the sample prepared by the following method.

By the empirical method, 2:4-dimethylthiazole etho-*p*-toluenesulphonate (31 g.), ethyl orthoformate, and pyridine were boiled together for 5 hours (Kodak Ltd. and Brooker, B.P. 408,273/1931). The product (6.23 g.) obtained by concentration in a vacuum, followed by precipitation with potassium iodide, was boiled out four times with methyl alcohol (15 c.c. \times 3, 25 c.c.). The fraction which crystallised from the first two extracts was combined with a second crop which resulted on concentration of the first three filtrates (total 5.2 g.). This was given a second fractional crystallisation from absolute alcohol (20 c.c., 25 c.c.) and methyl alcohol (15 c.c.) but this time there was no residue and the neocyanine crystallised in 18% yield (3.97 g.) (Found: I, 36.2%). In the first fractional crystallisation, the less soluble residue (0.46 g.) was combined with the dye which crystallised from the last two extracts (0.47 g.) and was recrystallised from methyl alcohol (100 c.c.), being obtained in 3% yield (0.6 g.) (Found: I, 30.3. Calc. for $C_{11}H_{21}N_3I_2S_2$: I, 30.2%). This is bis-2-(4-methyl-3-ethylthiazole)trimethincyanine iodide, identical with that prepared by Fisher and Hamer (J., 1930, 2502).

[Bis-2-(3-methyl- Δ^2 -thiazoline)][$\alpha\beta'$ -dimethin-2'-(3'-methyl- Δ^2 -thiazoline)]trimethincyanine Di-iodide (XVI; R = Me, X = I). — 3-Methyl-2-dianiloisopropylideneethiazolidine (0.64 g.; 1 mol.), 2-methyl- Δ^2 -thiazoline methiodide (1.07 g.; 2.2 mols.), and pyridine (8 c.c.) were heated together at 130–140° for 2 minutes. The washed dye (0.83 g.; 67% yield) was recrystallised from methyl alcohol (25 c.c.). The yield was 53% (0.65 g.) and after a second recrystallisation from methyl alcohol (40 c.c. per g.) it was 42% (Found: I, 40.95. $C_{17}H_{22}N_3I_2S_2$ requires I, 40.85%). When the purplish-red crystals were heated they began to shrink at about 115° and had largely melted and decomposed by 125° but there was no definite m. p. The absorption maximum was at 5065 Å. The dye sensitised a gelatino-bromide photographic emulsion up to 5900 Å.

[Bis-2-(3-ethyl- Δ^2 -thiazoline)][$\alpha\beta'$ -dimethin-2'-(3'-ethyl- Δ^2 -thiazoline)]trimethincyanine Diperchlorate (XVI; R = Et, X = ClO₄). — 3-Ethyl-2-dianiloisopropylideneethiazolidine (1.02 g.; 1 mol.), 2-methyl- Δ^2 -thiazoline ethiodide, and pyridine were heated together at 130–140° for 5 minutes. The gum, precipitated by absolute ether, was dissolved in hot spirit (30 c.c.) and treated with a hot solution of sodium perchlorate (1.68 g.; 4 mols.) in water (30 c.c.). The crude perchlorate (1.59 g.) was boiled out with and recrystallised from methyl alcohol (15 c.c., 225 c.c.), the product being obtained in 51% yield (0.93 g.) (Found: Cl, 11.7. $C_{30}H_{31}O_4N_3Cl_2S_2$ requires Cl, 11.65%). The brick-red crystals had m. p. 230° (decomp.). The absorption maximum was at 5060 Å. In a gelatino-bromide photographic emulsion the compound produced extra-sensitivity up to 5700 Å.

[Bis-4-(1-ethylquinoline)][$\alpha\beta'$ -dimethin-4'-(1'-ethylquinoline)]trimethincyanine Di-iodide. — Crude 1-ethyl-4-dianiloisopropylidene-1:4-dihydroquinoline (VIII) (0.75 g.; 1 mol.), lepidine ethiodide (1.20 g.; 2 mols.), and anhydrous sodium acetate (1.31 g.; 8 mols.) were ground together, treated with acetic anhydride (8 c.c.), and heated at 135–140° for 10 minutes. Brassy crystals of dye began to separate when the temperature reached 110°. The solid was filtered off, washed with acetic anhydride and with ether, ground with water (10 c.c.), washed with methyl alcohol, and boiled out with it three times (20 c.c. \times 3). The first fraction was rejected but the dye which crystallised from the second and third (0.01 g.) was put with the undissolved residue (0.41 g.) making a 27% yield (0.42 g.). On recrystallisation from methyl alcohol (1000 c.c. per g.) the yield was 20% (0.32 g.) (Found: I, 32.3. Calc. for $C_{38}H_{31}N_3I_2$: I, 32.15%). When samples of the original neocyanine ethiodide (Hamer, J., 1928, 1472), of the present synthetic dye, and of their mixture were heated, all melted simultaneously at 280° (decomp.).

We failed to isolate the dye when heating with pyridine took the place of heating with sodium acetate and acetic anhydride, but in another experiment 1-ethyl-4-dianiloisopropylidene-1 : 4-dihydroquinoline (0.19 g.; 1 mol.) and excess of lepidine ethiodide (0.45 g.; 3 mols.) were ground together, treated with ice-cold pyridine (2 c.c.), and left in the cold for six days, with occasional stirring. The crystals were filtered off and well washed; the residue (0.12 g.) was twice boiled out with methyl alcohol (15 c.c., 25 c.c.), and the product which crystallised (0.01 g.) added to what remained (0.02 g.), making up a 7% yield. After recrystallisation from methyl alcohol (30 c.c.), the yield of the characteristic brassy crystals was 2% (0.01 g.).

Bis-2-(5-chloro-3-ethylbenzthiazole)pentamethincyanine Iodide.—5-Chloro-2-methylbenzthiazole ethiodide (1.97 g.; 2 mols.) and β -anilinoacraldehyde anil hydrochloride (0.75 g.; 1 mol.) in boiling absolute alcohol (20 c.c.) were treated with a solution of sodium (0.14 g.; 2 atoms) in absolute alcohol (5 c.c.). The mixture was boiled and stirred for 3 minutes, during which time the solids dissolved and a green dye separated. After three recrystallisations of the washed dye (1.35 g.; 80% yield) from methyl alcohol (2600 c.c., 3900 c.c., and 5000 c.c. per g.) the yield was 38% (Found: 2Cl + I, 33.55. $C_{22}H_{21}N_2Cl_2IS_2$ requires 2Cl + I, 33.7%). The bluish-green crystals had m. p. 298° (decomp.). The absorption maximum was at 6560 Å. The dye sensitised a gelatino-bromide photographic emulsion from 6500—7400 Å., with a maximum at 7000 Å. This preparation was carried out by Dr. V. P. Pittman, whom we thank.

Bis-2-(4-methyl-3-ethylthiazole)pentamethincyanine Iodide.—2 : 4-Dimethylthiazole etho-*p*-toluenesulphonate (12.52 g.; 2 mols.), β -ethoxyacraldehyde diethyl acetal (3.84 g.; 1.1 mols.), and triethylamine (5.6 c.c.; 2 mols.) in pyridine (40 c.c.) were boiled and stirred together for 7 minutes. Ether precipitated a sticky solid which was dissolved in hot spirit and treated with a solution of potassium iodide (13 g.; 4 mols.) in hot water. The crude dye (2.3 g.) was boiled out with and recrystallised from absolute ethyl alcohol (15 c.c., 100 c.c.), being obtained in 21% yield (1.92 g.) (Found: I, 28.3. $C_{17}H_{23}N_2IS_2$ requires I, 28.45%). The steely bluish-green crystals had m. p. 214° (decomp.). The absorption curve had its maximum at 6370 Å. and an inflexion at 6050 Å. It sensitised from 6500—6900 Å. with the maximum at 6800 Å.

Bis-2-(3-ethyl- Δ^2 -thiazoline)pentamethincyanine Iodide.—A mixture of 2-methyl- Δ^2 -thiazoline ethiodide (3.98 g.; 2 mols.), β -anilinoacraldehyde anil hydrochloride (2 g.; 1 mol.), anhydrous potassium carbonate (5.36 g.; 5 mols.; 180-mesh), and ethyl alcohol (10 c.c.) was boiled for 4 minutes. The washed solid (1.71 g.) was recrystallised from methyl alcohol (10 c.c.) and obtained in 27% yield (0.88 g.). After a second recrystallisation from methyl alcohol (10 c.c.), the yield was 24% (0.77 g.) (Found: I, 30.2. $C_{18}H_{23}N_2IS_2$ requires I, 30.05%). The steely crystals had m. p. 231° (decomp.). The absorption maximum was at 5450 Å. The dye sensitised a gelatino-bromide photographic emulsion, the maximum lying at 5700 Å.

We are indebted to Miss M. D. Gauntlett for the absorption measurements and to Drs. B. H. Carroll and E. B. Knott for the sensitising tests.

KODAK LTD., WFALEDSTONE, HARROW, MIDDLESEX.

[Received, January 7th, 1947.]

272. The Galactomannan of the Lucerne Seed.

By E. L. HIRST, J. K. N. JONES, and WINIFRED O. WALDER.

The mucilaginous polysaccharide in the lucerne seed has been shown to consist of a galactomannan containing galactose and mannose in the approximate ratio of 2 to 1. Hydrolysis of the methylated polysaccharide gave a mixture of sugars among which 2 : 3 : 4 : 6-tetramethyl *d*-galactose, 2 : 4 : 6-trimethyl *d*-galactose, and 3 : 4-dimethyl *d*-mannose were detected. The general type of structure present in the polysaccharides is discussed on the basis of this evidence.

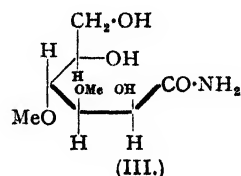
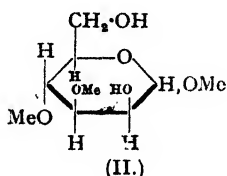
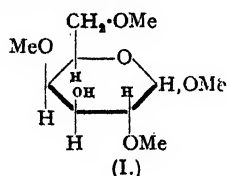
POLYSACCHARIDES other than cellulose are of common occurrence in the cell walls of many plants. They are, in general, insoluble in water but form solutions in dilute sodium hydroxide from which they may be precipitated by the addition of alcohol. Investigation of the hemicelluloses from cell walls, with special reference to the endosperm of ungerminated seeds, has revealed the presence of a number of different polysaccharides. Amongst these are the galactomannans which occur in the endosperm of the seeds of *Phoenix dactylifera*, *Elæis guineensis*, *Cocos nucifera*, *Coffea arabia* (Schulze, Steiger, and Maxwell, *Z. physiol. Chem.*, 1890, **14**, 227), and lucerne seed (May and Schulze, *Z. Biol.*, 1936, **97**, 201; Wise and Appling, *Ind. Eng. Chem. Anal.*, 1944, **16**, 28). Galactomannans have also been shown to occur in the seeds of the Fenugreek (Daoud, *Biochem. J.*, 1932, **26**, 255) and in the Carob bean (Spada, *Atte. Soc. Nat. Mat. Modena*, 1939, **70**, 20). It appears that these polysaccharides may function as reserve material in the seed and are utilised by the seed during germination (Schulze, *Landw. Jahrb.*, 1894, **23**, 1; *Ber. deut. bot. Ges.*, 1896, **14**, 66). In view of these observations and since some of the galactomannans have physical properties closely resembling those of the mucilages it was considered of interest to determine the mode of linkage of the sugars in the polysaccharide molecule.

The polysaccharide was isolated from lucerne seeds by the procedure given by Schulze

(*loc. cit.*). It was a white powder which did not reduce Fehling's solution and gave aqueous solutions of comparatively high viscosity. It underwent hydrolysis with boiling *N*-sulphuric acid at a rate indicating the presence of pyranose sugar residues in the molecule, and a quantitative determination of the sugars proved that *D*-mannose and *D*-galactose were present in the approximate ratio of 1 to 2. No other sugar could be detected.

The fully methylated galactomannan was obtained by reaction with sodium hydroxide and methyl sulphate followed by further treatment of the thallium hydroxide complex of the partially methylated derivative with methyl iodide.

The methylated polysaccharide, which was essentially homogeneous, was resistant to methyl-alcoholic hydrogen chloride. Hydrolysis was effected by use of a mixture of hydrochloric acid and glacial acetic acid which has been shown by Bell (*Biochem. J.*, 1935, 29, 2031) to be efficacious in the hydrolysis of resistant polysaccharides. The products were isolated as the methylglycosides, and on distillation fractions containing the following sugars were obtained: (1) 2:3:4:6-tetramethyl methyl-*D*-galactoside, identified after hydrolysis and formation of the characteristic crystalline anilide of tetramethyl *D*-galactose; (2) 2:4:6-trimethyl *D*-methylgalactoside (I), identified after hydrolysis as the crystalline sugar and as its crystalline anilide; and (3) 3:4-dimethyl *D*-methylmannoside (II), isolated after hydrolysis and oxidation as the crystalline 3:4-dimethyl *D*-mannonamide (III). Intermediate fractions were also obtained.



The isolation of these sugars proves that the galactomannan is not a mixture of a galactan and a mannan. This follows since a polysaccharide built of solely glycosidically linked mannose residues, some of which are present in a form having three points of linkage with other mannose residues, must possess a corresponding number of residues connected to others only by one linkage. The experimental results show clearly that no such mannose end groups are present, and it follows that the mannose residues must be present in a structure containing galactose also. The sugar residues isolated are all in the pyranose form and are substituted on C_4 by a methoxyl group. The isolation of a large amount of 2:3:4:6-tetramethyl *D*-galactose (*ca.* 30%) proves that the polysaccharide is of the branched-chain type and that half the galactose residues are terminal groupings. Unfortunately, the exact ratios of 2:4:6-trimethyl *D*-galactose and 3:4-dimethyl *D*-mannose could not be accurately determined in these experiments since some of the intermediate fractions which had not been fully examined were lost by enemy action. Nevertheless, an inspection of the methoxyl figures indicates that the relative molecular proportions of 2:3:4:6-tetramethyl methyl-*D*-galactoside, trimethyl methylhexoside, and dimethyl methylhexoside are 1:1:1. At least one-third of the dimethyl methylhexoside is known to be 3:4-dimethyl methylmannoside, and at least one-third of the trimethyl methylhexoside is 2:4:6-trimethyl methylgalactoside. A further investigation will be necessary in order to determine whether or not other sugars are present amongst the products of hydrolysis. In the meantime it is clear that half the galactose residues are attached in the form $\text{Gal} \dots$ and therefore are end groups. Another set of galactose residues is present in the form $\dots 3\text{Gal} \dots$, linked through positions 1 and 3, and at least one-third of the mannose residues occur as $\dots \frac{6\text{M}}{2} \dots$, linked through positions 1, 2, and 6.

It will be observed that the 1:3 galactose linkage so common in polysaccharides containing galactose, and the 1:6 and 1:2 mannose linkages occurring in damson gum, cherry gum (Hirst, *J.*, 1942, 70), and yeast mannan (Haworth, Hirst, and Isherwood, *J.*, 1937, 784; Haworth, Hart, and Peat, *J.*, 1941, 833), also occur in this galactomannan.

EXPERIMENTAL.

(All temperatures recorded for distillations are bath temperatures).

Lucerne seeds (500 g.) were finely ground and heated at 100° for 8 hours, with continuous stirring, with 10% potassium hydroxide solution (4 l.) until a jelly-like mass was formed and no more ammonia was evolved. The alkaline solution was then poured with stirring into alcohol (8 l.), and the dark solid which separated was washed with alcohol by decantation and filtered off. The precipitate was

purified by reprecipitation from water with alcohol. Insoluble cell-wall material was then removed by heating the solid with potassium hydroxide solution (4 l.) for 3 hours, cooling, and centrifuging. The insoluble residues were extracted repeatedly until the extracts gave no precipitate on addition of alcohol. The combined extracts were then poured into alcohol (4 vols.) and the precipitate was filtered off and further purified by reprecipitation from acidified aqueous solution (hydrochloric acid) with alcohol.

Traces of starch were removed from the polysaccharide by the action of "taka-diastase" (0.05%) at 37° for 12 hours. Further purification was achieved by precipitation of the copper complex by the addition of copper sulphate solution to a hot alkaline solution of the crude polysaccharide until no further material was precipitated. The copper complex was washed well with hot water and filtered off. The complex was decomposed by grinding it with alcohol containing hydrochloric acid, and the regenerated polysaccharide was ground and washed with alcohol until free from copper and chloride ions. Finally, the product was purified by dissolving it in water and precipitating it from the aqueous solution with alcohol, and dried in vacuum. Yield, 10 g. of a white powder, which dissolved in water to form viscous non-reducing solutions; $[\alpha]_D^{20} + 89^\circ$ (Found: furfuraldehyde, 2; uronic acid, nil; N, nil; mannose, determined as the phenylhydrazone after hydrolysis with *N*-sulphuric acid at 95° for 2½ hours, 29.6; galactose, determined as the phenylmethylhydrazone after the same treatment, 58%; equiv. by titration with 0.1*N*-sodium hydroxide, 4540).

Methylation of the Polysaccharide.—The pure polysaccharide (25 g.) was dissolved in water (300 c.c.) and 30% sodium hydroxide (400 c.c.), and methylated with methyl sulphate (200 c.c.) added in portions (30 c.c.) at 20 minute intervals. The methylation was carried out in an atmosphere of nitrogen and with the usual precautions. After 24 hours the cooled solution was partly neutralised with dilute sulphuric acid and concentrated under reduced pressure. The residue was then re-methylated using the conditions described above. Two repetitions of this process gave a crude methylated product (isolated in the usual manner) which was freed from sodium sulphate and other salts by dialysis. Yield, 15.5 g. (Found: OMe, 34.0%). To complete the methylation the product was dissolved in ethyl alcohol (100 c.c.) and benzene (100 c.c.), and a solution of thallium ethoxide (1.7*N*, 100 c.c.) in benzene added. Solvent was removed under reduced pressure and the residual solid finely powdered (150 mesh) and boiled under reflux with methyl iodide (150 c.c.) for 30 hours. Excess of methyl iodide was boiled off and the residual solid extracted exhaustively with acetone. Concentration of the extracts gave a residue of partially methylated galactomannan (15 g.) (Found: OMe, 36.2%). This methylation process with thallium ethoxide and methyl iodide was repeated (see above), and the isolated product (13 g.) methylated with silver oxide (10 g.) and methyl iodide (30 c.c.). Repetition of this process gave a product (13 g.) (Found: OMe, 43.5%) isolated in the usual manner.

Fractionation of the Methylated Polysaccharide.—The methylated polysaccharide (10.1 g.) was fractionally precipitated from chloroform by the addition of light petroleum (b. p. 40–60°) giving: Fraction I (2.1 g.), a white solid, $[\alpha]_D^{20} + 72^\circ$ (c. 1.0 in chloroform) (Found: OMe, 43.4%; furfuraldehyde, nil); Fraction II (6.0 g.), a white solid, $[\alpha]_D^{20} + 71^\circ$ (c. 1.1 in chloroform) (Found: OMe, 43.2%; furfuraldehyde, nil); Fraction III (0.9 g.), a white solid, $[\alpha]_D^{20} + 69^\circ$ (c. 0.9 in chloroform) (Found: OMe, 44.1%; furfuraldehyde, nil); Fraction IV (1.0 g.), a sticky solid.

Hydrolysis of the Methylated Polysaccharide.—Hydrolysis of the methylated material was difficult as the product was relatively stable to boiling methyl-alcoholic hydrogen chloride and to hot *N*-hydrochloric acid. The following procedure was eventually adopted as the most satisfactory technique. The methylated polysaccharide (7.3 g., Fractions I and II) was dissolved in a mixture of glacial acetic acid (50 c.c.), water (25 c.c.), and concentrated hydrochloric acid (25 c.c.), and heated at 100° for 6 hours. Changes in optical rotation were not observable, but preliminary experiments had shown that the hydrolysis was complete at the end of this time. Barium carbonate was added to the cooled solution until a test portion of the solution gave a grey and not a blue colour to Congo-red paper. The solution was then filtered and evaporated to dryness under reduced pressure. The solid residue was then extracted with chloroform, and the extracts were concentrated and boiled with methyl-alcoholic hydrogen chloride (3% w/v) for 12 hours. The cooled solution was then neutralised with silver carbonate and filtered, and the filtrate was concentrated under reduced pressure at 40° to a syrup (6.4 g.) which was fractionally distilled in a vacuum giving: Fraction i (0.86 g.), b. p. 90°/0.001 mm., $n_D^{15} 1.4539$ (Found: OMe, 59.5%); Fraction ii (0.72 g.), b. p. 108°/0.001 mm., $n_D^{15} 1.4522$ (Found: OMe, 61.9%); Fraction iii (0.53 g.), b. p. 110°/0.001 mm., $n_D^{15} 1.4542$ (Found: OMe, 60.0%); Fraction iv (0.57 g.), b. p. 120°/0.01 mm., $n_D^{15} 1.4560$ (Found: OMe, 53.8%); Fraction v (1.40 g.), b. p. 130°/0.001 mm., $n_D^{15} 1.4601$ (Found: OMe, 48.8%); Fraction vi (1.32 g.), b. p. 160°/0.001 mm., $n_D^{15} 1.4680$ (Found: OMe, 41.8%); Fraction vii (0.57 g.), b. p. 170°/0.01 mm., $n_D^{15} 1.4780$ (Found: OMe, 41.9%); residue, 0.43 g.

Hydrolysis of the Fractions.—The first three fractions having very similar methoxyl values were combined (2.1 g.) and hydrolysed by heating with 2*N*-hydrochloric acid at 95° for 3 hours; $[\alpha]_D^{20}$ (initial value not observable), $+ 71^\circ$ (2 hours); $+ 105^\circ$ (3 hours, constant value). The solution was cooled, neutralised with barium carbonate, and filtered, the filtrate concentrated under reduced pressure, and the residue exhaustively extracted with chloroform. Concentration of the extracts gave a syrup (1.9 g.) which was at least 94% 2 : 3 : 4 : 6-tetramethyl *D*-galactose; $[\alpha]_D^{20} + 109^\circ$ (in water) (Found: OMe, 52.2. Calc. for $C_{16}H_{26}O_6$: OMe, 51.8%). The sugar (0.32 g.), on being heated under reflux with aniline (0.1 c.c.) dissolved in alcohol (3 c.c.) for 2½ hours, gave 2 : 3 : 4 : 6-tetramethyl *D*-galactose anilide (0.34 g.), m. p. 189°, not depressed on admixture with an authentic sample. Fraction iv (0.56 g.) was hydrolysed by boiling with 2*N*-hydrochloric acid (25 c.c.) for 3 hours; $[\alpha]_D^{20} + 56^\circ$ (2 hours); $+ 70^\circ$ (3 hours, constant value). The sugar (0.5 g.) was isolated as described above; $[\alpha]_D^{20} + 70^\circ$ (c. 1.0 in water) (Found: OMe, 40.0. Calc. for $C_6H_{12}O_5$: OMe, 41.8%). On standing, the syrup partly crystallised. The crystals were separated by trituration with ether and had m. p. 105°, not depressed on admixture with an authentic specimen of 2 : 3 : 4 : 6-trimethyl *D*-galactose. The syrup (0.4 g.) on boiling with aniline (0.3 g.) in ethyl alcohol (2 c.c.) for 2½ hours gave the anilide of 2 : 3 : 4 : 6-trimethyl *D*-galactose (0.5 g.), m. p. 179°, not depressed on admixture with an authentic specimen. At the most only traces of 2 : 3 : 6-trimethyl *D*-galactose could be present in the syrup, as on standing with cold 5% methyl-alcoholic hydrogen chloride no downward change of rotation was observable; $[\alpha]_D^{20} + 41^\circ$ (initial

value); + 49° (3 hours); + 58° (6 hours). Fraction vii (0.57 g.) was hydrolysed with boiling 2*N*-hydrochloric acid; $[\alpha]_D^{20} + 31^\circ$ (initial value); 0° (3 hours, constant value). The solution was cooled and neutralised with barium carbonate, and the filtrate was evaporated to dryness. The syrup (0.5 g.), isolated in the usual manner, did not crystallise. The absence of any derivative of mannose or galactose with a hydroxyl group on C₄ was indicated by the fact that the syrup (0.03 g.) in methylalcoholic hydrogen chloride (5 c.c.; 5%) showed no change of rotation (+ 10°) in 7 days. The syrup (0.2 g.) was oxidised with bromine water at 45° until non-reducing (7 hours). The cooled solution was neutralised with silver carbonate and filtered, and silver ions were removed with hydrogen sulphide. The filtered solution was concentrated to a syrup (0.15 g.) which did not crystallise. Accordingly, the material was dissolved in liquid ammonia and excess of ammonia allowed to evaporate. The residue crystallised, and by trituration with acetone 3:4-dimethyl *d*-mannonamide, m. p. 139°, not depressed on admixture with an authentic specimen, was isolated. The amide gave a strong positive test for an α -hydroxy-amide by the method of Weerman.

A complete examination of Fractions v and vi was not possible since these fractions were lost by enemy action. They obviously contained some 2:4:6-trimethyl *d*-galactose and 3:4-dimethyl *d*-mannose, but at this stage the presence of other galactose and mannose derivatives cannot be excluded.

We wish to thank Mr. L. J. Breddy for assistance in the preparation of the galactomannan.

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[Received, January 7th, 1947.]

273. Preparation and Properties of Allyl Phosphines, Arsines, and Stannanes.

By W. J. JONES, W. C. DAVIES, S. T. BOWDEN, C. EDWARDS, V. E. DAVIS, and L. H. THOMAS.

Phosphines, arsines, and stannanes containing allyl and methylallyl groups have been produced by means of the Grignard reaction, their physical properties have been examined, and characteristic derivatives have been prepared.

No phosphine containing either an allyl or a methylallyl group has hitherto been prepared, though Hofmann (*Phil. Trans.*, 1860, 150, 412) records that he experimented unsuccessfully on the effect of heating phosphorus, zinc, and allyl iodide together in a sealed tube, but phenyl-*p*-tolylmethylallylphosphonium iodide has been obtained by Pope and Gibson (*J.*, 1912, 101, 737; also Radcliffe and Brindley, *J. Soc. Chem. Ind.*, 1923, 42, 66) by the combination of phenyl-*p*-tolylmethylphosphine with allyl iodide, and trisdiphenylallylphosphonium bromide by Worral (*J. Amer. Chem. Soc.*, 1930, 52, 2936) by the union of trisdiphenylphosphine and allyl bromide. Such phosphines have now been prepared by the Grignard method, *triallylphosphine* and *phenyl*-, *p*-tolyl-, *p*-xylyl-, *p*-ethylphenyl-, *p*-isopropylphenyl-, *p*-methoxyphenyl-, *p*-phenoxyphenyl-, and *p*-bromophenyl-diallylphosphine from allylmagnesium bromide, and *tri*- β -methylallylphosphine and *phenyl*-, *p*-tolyl-, *p*-xylyl-, *p*-ethylphenyl-, *p*-isopropylphenyl-, *p*-methoxyphenyl-, and *p*-bromophenyl-di- β -methylallylphosphine from β -methylallylmagnesium bromide.

Triallylsarsine has been obtained by Gryszkiewicz-Trochimowski and Zambrzycki (*Rocz. Chem.*, 1926, 6, 794). *Phenyldiallylsarsine* has now been prepared from allylmagnesium bromide, and *tri*- β -methylallylsarsine and *phenyldi*- β -methylallylsarsine from β -methylallylmagnesium bromide.

Tetra-allyltin has been described by Vijayraghavan (*J. Indian Chem. Soc.*, 1945, 22, 119), and allylstannonic acid and allylpentachlorostannic acid by Lesbre and Glotz (*Compt. rend.*, 1934, 198, 1427). *Triethylallyltin*, *diethyldiallyltin*, *tri*-*n*-butylallyltin and *di*-*n*-butyldiallyltin have been prepared in the present work from allylmagnesium bromide.

In order to secure good yields, it has been found necessary to employ the Grignard reagent in excess over the chlorophosphine, chloroarsine, or chlorostannane, to exclude air rigorously during the preparation, and to distil the product under low pressure. In the reaction, diallyl, *b. p.* 59.5°, or di- β -methylallyl, *b. p.* 113°, is formed as by-product through the coupling action of the Grignard reagent, but the hydrocarbon is easily separated, after the ether, by distillation from the phosphine, arsine, or stannane.

The allylphosphines rapidly oxidise in contact with air. They combine with mercuric chloride to give mercurichlorides of the general formula PR_3HgCl_2 , with benzoquinone to produce pale yellow addition compounds $\text{PR}_3\text{C}_6\text{H}_4\text{O}_2$, with carbon disulphide to yield either intensely red compounds PR_3CS_2 or red colorations in solution, and with methyl iodide to give the methylphosphonium iodides. These methiodides combine with mercuric iodide to

form yellow complex mercuri-iodides $\text{PR}_4\text{I}, \text{HgI}_2$, and with cadmium iodide to give cadmi-iodides $(\text{PR}_4\text{I})_2, \text{CdI}_2$. The allylarsines closely resemble the phosphines chemically, and the allylstannanes also are rapidly attacked by air.

In the absence of air, the allyl-phosphines, -arsines, and -stannanes are thermally stable, being unaffected even on being kept at 250° for an hour. A comparison of the b. p./50 mm. with that of the corresponding *n*-alkyl compound is made in the following table, from which it will be seen that the difference is slight.

Phosphine.	B. p./50 mm.	Phosphine.	B. p./50 mm.
Triallyl	98°	Tri- <i>n</i> -propyl	103°
Phenyldiallyl	160	Phenyldi- <i>n</i> -propyl	159
<i>p</i> -Tolyldiallyl	171	<i>p</i> -Tolyldi- <i>n</i> -propyl	174
<i>p</i> -Xylyldiallyl	179	<i>p</i> -Xylyldi- <i>n</i> -propyl	180
<i>p</i> -Ethylphenyldiallyl	188	<i>p</i> -Ethylphenyldi- <i>n</i> -propyl	181
Tri- β -methylallyl	142	Tri- <i>n</i> -butyl	149
Phenyldi- β -methylallyl	184	Phenyldi- <i>n</i> -butyl	185
<i>p</i> -Tolyldi- β -methylallyl	190	<i>p</i> -Tolyldi- <i>n</i> -butyl	197
<i>p</i> -Xylyldi- β -methylallyl	200	<i>p</i> -Xylyldi- <i>n</i> -butyl	204
<i>p</i> -Ethylphenyldi- β -methylallyl ...	205	<i>p</i> -Ethylphenyldi- <i>n</i> -butyl	209
Arsine.		Arsine.	
Triallyl	111	Tri- <i>n</i> -propyl	110
Phenyldiallyl	171	Phenyldi- <i>n</i> -propyl	165
Tri- β -methylallyl	143	Tri- <i>n</i> -butyl	155
Phenyldi- β -methylallyl	189	Phenyldi- <i>n</i> -butyl	193
Stannane.		Stannane.	
Triethylallyl	112	Triethyl- <i>n</i> -propyl	112

As is shown in the next table, the average difference between the molecular volumes (in c.c.) of an aryldiallylphosphine and its corresponding aryldi- β -methylallylphosphine at 25° is 34.0 c.c., compared with 33.0 c.c. for two CH_2 groups in the higher trialkylphosphines (Jackson, Davies, and Jones, *J.*, 1931, 2109).

Phosphine.	Diallyl.	Di- β -methylallyl.	Diff.
Phenyl	196.2	230.2	34.0
<i>p</i> -Tolyl	211.5	246.5	35.0
<i>p</i> -Xyllyl	227.6	262.0	34.4
<i>p</i> -Ethylphenyl	230.0	263.2	33.2
<i>p</i> -isoPropylphenyl	248.0	280.6	32.6
<i>p</i> -Methoxyphenyl	216.2	249.6	33.4
<i>p</i> -Bromophenyl	210.6	245.8	35.2

The Lorenz-Lorentz molecular refractivities, $(n^2 - 1)M/(n^2 + 2)d$, of the allyl phosphines for sodium D light are given in the following table. The calculated values have been obtained by means of the constants given by Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 605), together with those given for phosphorus by Jones, Davies, and Dyke (*J. Physical Chem.*, 1933, **37**, 594).

$[M_L]_D$.			$[M_L]_D$.		
Diallylphosphine.	Found.	Calc.	Di- β -methylallylphosphine.	Found.	Calc.
Phenyl	64.08	63.99	Phenyl	73.16	73.23
<i>p</i> -Tolyl	68.25	68.99	<i>p</i> -Tolyl	78.11	78.24
<i>p</i> -Xyllyl	72.95	73.35	<i>p</i> -Xyllyl	82.84	82.58
<i>p</i> -Ethylphenyl	73.78	73.82	<i>p</i> -Ethylphenyl	83.03	83.05
<i>p</i> -isoPropylphenyl	78.24	78.44	<i>p</i> -isoPropylphenyl	87.36	87.67
<i>p</i> -Methoxyphenyl	70.97	70.83	<i>p</i> -Methoxyphenyl	79.65	80.07
<i>p</i> -Phenoxyphenyl	89.47	89.76	<i>p</i> -Bromophenyl	81.23	80.99

The phosphines, arsines, and stannanes are freely soluble in ether, alcohol, benzene, or carbon tetrachloride, but not in water. The molecular weights, M , of the phosphines have been determined by the cryoscopic method in benzene solution, and found to be normal.

EXPERIMENTAL.

Preparation of the Phosphines.—The necessary dichlorophosphines, phenyl b. p. $221-222^\circ$, *p*-tolyl b. p. $100^\circ/12$ mm., *p*-xyllyl b. p. $133^\circ/16$ mm., *p*-ethylphenyl b. p. $133^\circ/18$ mm., *p*-isopropylphenyl b. p. $132-134^\circ/14$ mm., *p*-methoxyphenyl b. p. $153^\circ/21$ mm., *p*-phenoxyphenyl b. p. $200^\circ/12$ mm., and *p*-bromophenyl b. p. $135-136^\circ/14$ mm., were prepared by the method of Michaelis (*Ber.*, 1879, **12**, 1009; *Annalen*, 1896, **293**, 223) and isolated either by the distillation method of Grüttner and Wiernik (*Ber.*, 1915, **48**, 1475) or by the extraction method of Davies (*J.*, 1935, 463). Allyl bromide,

b. p. 70–71°, was prepared as described in *Org. Synth.*, I, 24. To prepare β -methylallyl bromide, phosphorus tribromide (45 c.c.) was added dropwise with exclusion of moisture during 5 hours with periodic shaking to dried (CaO), freshly-distilled β -methylallyl alcohol (118 c.c.) in dried (KOH), freshly-distilled pyridine (32 c.c.) cooled with ice-salt: the reaction mixture was filtered, and the filtrate on distillation gave β -methylallyl bromide, b. p. 94–95° (85 g.). Both bromides after drying (P_2O_5 or $CaCl_2$) were used immediately, after a fresh distillation, for the preparation of the phosphines.

To 1½ mols. (36.5 g.) of finely divided magnesium a granule of iodine and 100 c.c. of absolute ether, contained in a dried round-bottom flask fitted with a mechanical stirrer, dropping funnel, reflux condenser, siphon tube, and a gas-inlet tube, through which dry hydrogen was passed, there was added, dropwise in the course of about 2 hours so as to maintain a gentle boiling, ½ mol. of allyl bromide (42 c.c.) or of β -methylallyl bromide (51 c.c.) in 285 c.c. of ether (Gilman and McGlumphy, *Bull. Soc. chim.*, 1928, 43, 1322). After an hour's standing, the Grignard solution was siphoned quickly through a glass-wool filter into a second round-bottom flask provided with similar fittings to the first, and, with continuous stirring, passage of hydrogen and external cooling with ice, thereto was added gradually in ether (100 c.c.) 1/12 mol. of phosphorus trichloride (7.1 c.c.) or 1/8 mol. of the aryldichlorophosphine [phenyl (17 c.c.), *p*-tolyl (19 c.c.), *p*-xylyl (21 c.c.), *p*-ethylphenyl (21 c.c.), *p*-isopropylphenyl (22 c.c.), *p*-methoxyphenyl (20 c.c.), *p*-phenoxyphenyl (24 c.c.), or *p*-bromophenyl (19 c.c.)]. After the addition, the mixture was boiled for ½ hour, again cooled to 0°, and then ammonium chloride (50 g.) in water (250 c.c.) was added gradually through the dropping-funnel until all the precipitated magnesium salts had dissolved. The resulting mixture was siphoned under carbon dioxide into a separating funnel, and the ether layer was dried (Na_2SO_4) in a stoppered bottle. The dried solution was distilled in carbon dioxide to remove ether and diallyl or di- β -methylallyl, and the residual phosphine was redistilled in carbon dioxide under low pressure and preserved in sealed glass tubes. All subsequent manipulations of the phosphine were carried out under carbon dioxide.

Triallylphosphine.—This compound was prepared from allylmagnesium bromide and phosphorus trichloride: the liquid (4 g.) had b. p. 69°/13 mm. (Found: C, 70.1; H, 10.0; P, 19.7. $C_9H_{14}P$ requires C, 70.1; H, 9.8; P, 20.1%). Mercuric chloride added to the phosphine in alcohol precipitated the *mercurichloride*, rhomboids, in. p. 135° (Found: Cl, 16.9; P, 7.2. $C_9H_{14}P.HgCl_2$ requires Cl, 16.7; P, 7.3%). This and all the succeeding mercurichlorides, mercuri-iodides and cadmi-iodides were repeatedly recrystallised to constant m. p. from alcohol, except where another solvent is stated.

The phosphine (1 c.c.) in alcohol (20 c.c.) mixed with *p*-benzoquinone (0.4 g.) in alcohol (20 c.c.) produced a red coloration, and after standing, the addition of ether precipitated pale-yellow stellate crystals of *triallylphosphine-p-benzoquinone*, which darkened at 100° and became black at 130° (Found: C, 69.1; H, 7.5. $C_{15}H_{18}O_2P$ requires C, 68.7; H, 7.3%). Excess of carbon disulphide added to the phosphine (2 c.c.) in alcohol (5 c.c.) gave a dark red coloration, and on cooling to 0° *triallylphosphine-carbondisulphide* separated as red needles, m. p. 32.5°, unstable in the air (Found: C, 51.7; H, 6.9. $C_{11}H_{14}PS_2$ requires C, 52.1; H, 6.6%). Mixed in the absence of air, the phosphine and methyl iodide in ether immediately gave a precipitate of *methyltriallylphosphonium iodide*, pearly flakes from alcohol-ether (Found: I, 42.7. $C_{10}H_{14}PI$ requires I, 42.9%).

Phenyldiallylphosphine.—This compound (8 g.) was obtained by the interaction of allylmagnesium bromide and phenyldichlorophosphine and had b. p. 127°/14 mm., d_4^{25} 0.9693, n_D^{25} 1.5670 (Found: C, 75.5; H, 8.1. $C_{12}H_{16}P$ requires C, 75.7; H, 8.0%). It formed the *mercurichloride*, needles, m. p. 123° (Found: Cl, 15.6. $C_{12}H_{16}P.HgCl_2$ requires Cl, 15.4%).

***p*-Tolyldiallylphosphine.**—The phosphine (7 g.) was produced from allylmagnesium bromide and *p*-tolylchlorophosphine and had b. p. 138°/14 mm., d_4^{25} 0.9651, n_D^{25} 1.5545 (Found: C, 75.9; H, 8.9. $C_{13}H_{17}P$ requires C, 76.4; H, 8.4%). It yielded the *mercurichloride*, elongated prisms, m. p. 110.5° (Found: Cl, 14.9. $C_{13}H_{17}P.HgCl_2$ requires Cl, 14.9%).

***p*-Xylyldiallylphosphine.**—The interaction of the allyl Grignard reagent and *p*-xylyldichlorophosphine gave the phosphine (16 g.), which had b. p. 144°/13 mm., d_4^{25} 0.9584, n_D^{25} 1.5540 (Found: C, 76.6; H, 8.8; P, 14.0; M, 223. $C_{14}H_{18}P$ requires C, 77.0; H, 8.8; P, 14.2%; M, 218). The *mercurichloride* crystallised in rhomboids, m. p. 170° (Found: Cl, 14.9; P, 6.3. $C_{14}H_{18}P.HgCl_2$ requires Cl, 14.5; P, 6.3%).

***p*-Ethylphenyldiallylphosphine.**—Obtained from allylmagnesium bromide and *p*-ethylphenyldichlorophosphine, the phosphine (16 g.) had b. p. 145°/10 mm., d_4^{25} 0.9484, n_D^{25} 1.5545 (Found: C, 76.7; H, 9.0. $C_{14}H_{18}P$ requires C, 77.0; H, 8.8%).

***p*-isopropylphenyldiallylphosphine.**—This compound (16 g.) was prepared from allylmagnesium bromide and *p*-isopropylphenyldichlorophosphine and had b. p. 153°/11 mm., d_4^{25} 0.9361, n_D^{25} 1.5435 (Found: C, 77.5; H, 9.1; M, 242. $C_{15}H_{20}P$ requires C, 77.5; H, 9.1%; M, 232). It yielded the *mercurichloride*, m. p. 47°, from glacial acetic acid (Found: Cl, 14.6. $C_{15}H_{20}P.HgCl_2$ requires Cl, 14.1%).

***p*-Methoxyphenyldiallylphosphine.**—This phosphine (12 g.), produced from allylmagnesium bromide and *p*-methoxyphenyldichlorophosphine, had b. p. 162°/15 mm., d_4^{25} 1.0189, n_D^{25} 1.5705 (Found: C, 70.6; H, 8.1. $C_{13}H_{18}OP$ requires C, 70.9; H, 7.8%). Its *mercurichloride* separated in prisms, m. p. 131° (Found: Cl, 14.8. $C_{13}H_{18}OP.HgCl_2$ requires Cl, 14.4%).

***p*-Phenoxyphenyldiallylphosphine.**—Obtained by the action of the allyl Grignard reagent on *p*-phenoxyphenyldichlorophosphine, this phosphine (12 g.) had b. p. 238°/15 mm., d_4^{25} 1.0847, n_D^{25} 1.6040 (Found: C, 76.2; H, 7.1; P, 10.9; M, 278. $C_{15}H_{18}OP$ requires C, 76.6; H, 6.8; P, 11.0%; M, 282). The *mercurichloride*, difficultly soluble in alcohol and ether, became black at 210° (Found: Cl, 13.2. $C_{15}H_{18}OP.HgCl_2$ requires Cl, 12.8%).

***p*-Bromophenyldiallylphosphine.**—The allyl Grignard reagent and *p*-bromophenyldichlorophosphine gave the phosphine (15 g.), b. p. 186°/37 mm., d_4^{25} 1.2783 (Found: C, 53.1; H, 5.5; P, 11.4; M, 272. $C_{11}H_{11}BrP$ requires C, 53.5; H, 5.2; P, 11.5%; M, 269). The *mercurichloride* crystallised in needles, m. p. 108° (Found: P, 5.7. $C_{11}H_{11}BrP.HgCl_2$ requires P, 5.7%).

Tri- β -methylallylphosphine.—This tertiary phosphine (5 g.) was prepared through the interaction of β -methylallylmagnesium bromide and phosphorus trichloride and had b. p. 112°/15 mm. (Found:

C, 73.1; H, 11.0; P, 15.4; M, 196. $C_{15}H_{21}P$ requires C, 73.4; H, 10.8; P, 15.8%; M, 196. It immediately oxidised in the air to form the *oxide*, needles, m. p. 132°, from ether (Found: C, 67.6; H, 10.2. $C_{15}H_{21}OP$ requires C, 67.9; H, 10.0%); the same compound was also produced from β -methylallylmagnesium bromide and phosphorus oxychloride. In the absence of air the phosphine and mercuric chloride in alcohol gave *tri- β -methylallylphosphine mercurichloride*, rhombic plates, m. p. 162° (Found: Cl, 15.2. $C_{15}H_{21}P.HgCl_2$ requires Cl, 15.2%). *Methyltri- β -methylallylphosphonium iodide*, from its components in ether, formed needles, m. p. 151°, from alcohol-ether (Found: I, 37.4. $C_{15}H_{24}PI$ requires I, 37.5%). *Tri- β -methylallylphosphine-p-benzoquinone*, precipitated by ether from mixed alcoholic solutions of its components, formed pale lemon-yellow stellate crystals, which darkened in the air or on heating, becoming black at 200° (Found: C, 70.8; H, 8.5. $C_{15}H_{25}O_2P$ requires C, 71.0; H, 8.3%).

Phenyldi- β -methylallylphosphine.—The compound (15 g.) was obtained from the Grignard reagent and phenyldichlorophosphine, and had b. p. 148°/13 mm., d_4^{25} 0.9484, n_D^{25} 1.5485 (Found: C, 76.8; H, 9.0; P, 14.2; M, 223. $C_{14}H_{19}P$ requires C, 77.0; H, 8.8; P, 14.2%; M, 218). It gave the *mercurichloride*, rectangular plates, m. p. 140.5° (Found: Cl, 14.7. $C_{14}H_{19}P.HgCl_2$ requires Cl, 14.5%). *Phenylmethyldi- β -methylallylphosphonium iodide* separated in needles, m. p. 188° (decomp.), from alcohol-ether (Found: I, 34.9. $C_{15}H_{22}PI$ requires I, 35.2%). On mixing hot alcoholic solutions of mercuric iodide and excess of the methiodide, *phenylmethyldi- β -methylallylphosphonium mercuri-iodide* crystallised out on cooling as lemon-coloured needles, m. p. 133° (Found: I, 47.0; Hg, 24.5. $C_{15}H_{22}PI.HgI_2$ requires I, 46.7; Hg, 24.6%). Similarly, cadmium iodide and the methiodide gave the *cadmi-iodide*, needles, m. p. 114° [Found: I, 46.7; Cd, 10.5. $(C_{15}H_{22}PI)_2.CdI_2$ requires I, 46.7; Cd, 10.3%]. Addition of excess of bromine to the phosphine in ether gave a precipitate, which, on solution in hot alcohol and treatment with water until turbidity appeared, yielded *phenyldi-(β -dibromo- β -methylpropyl)phosphine oxide*, needles, m. p. 105°, from aqueous alcohol (Found: Br, 57.6. $C_{14}H_{19}OBr_2P$ requires Br, 57.7%).

p-Tolyldi- β -methylallylphosphine.—Prepared from the β -methylallyl Grignard reagent and *p*-tolyl-dichlorophosphine, the phosphine (11 g.) had b. p. 168°/23 mm., d_4^{25} 0.9426, n_D^{25} 1.5465 (Found: C, 77.4; H, 9.3; P, 13.3; M, 228. $C_{15}H_{21}P$ requires C, 77.5; H, 9.1; P, 13.4%; M, 232). It gave the *mercurichloride*, cubes, m. p. 164° (Found: Cl, 14.2. $C_{15}H_{21}P.HgCl_2$ requires Cl, 14.1%). *p-Tolyldi- β -methylallylphosphonium iodide* crystallised in needles, m. p. 94°, from alcohol-ether (Found: I, 33.8. $C_{16}H_{24}PI$ requires I, 33.9%) and yielded *p-tolylmethyldi- β -methylallylphosphonium mercuri-iodide*, pale-yellow prisms, m. p. 79° (Found: I, 46.1; Hg, 24.1. $C_{16}H_{24}PI.HgI_2$ requires I, 45.9; Hg, 24.2%).

p-Xylyldi- β -methylallylphosphine.—The phosphine (12 g.) was obtained from β -methylallylmagnesium bromide and *p*-xylyldichlorophosphine; it had b. p. 166°/16 mm., d_4^{25} 0.9402, n_D^{25} 1.5450 (Found: C, 77.8; H, 9.4; P, 12.3. $C_{15}H_{23}P$ requires C, 78.0; H, 9.4; P, 12.6%). The *mercurichloride* separated in prisms, m. p. 201—202° (Found: Cl, 13.7. $C_{15}H_{23}P.HgCl_2$ requires Cl, 13.7%). *p-Xylylmethyldi- β -methylallylphosphonium iodide* crystallised in prisms, m. p. 161°, from alcohol-ether (Found: I, 32.5. $C_{17}H_{25}PI$ requires I, 32.7%). It gave with mercuric iodide in alcohol the *mercuri-iodide*, pale yellow rhombic plates, m. p. 71° (Found: I, 45.5; Hg, 23.6. $C_{17}H_{25}PI.HgI_2$ requires I, 45.2; Hg, 23.8%), and with cadmium iodide, the *cadmi-iodide*, needles, m. p. 159° [Found: I, 44.0; Cd, 10.2. $(C_{17}H_{25}PI)_2.CdI_2$ requires I, 44.4; Cd, 9.8%].

p-Ethylphenyldi- β -methylallylphosphine.—This compound (12 g.), prepared from the Grignard reagent and *p*-ethylphenyldichlorophosphine, had b. p. 178°/20 mm., d_4^{25} 0.9360, n_D^{25} 1.5435 (Found: C, 77.7; H, 9.6; P, 12.4; M, 240. $C_{16}H_{23}P$ requires C, 78.0; H, 9.4; P, 12.6%; M, 246). The *mercurichloride* separated in prisms, m. p. 156° (Found: Cl, 14.1. $C_{16}H_{23}P.HgCl_2$ requires Cl, 13.7%). *p-Ethylphenylmethyldimethyl- β -allylphosphonium iodide*, rectangular plates, m. p. 153°, from alcohol-ether (Found: I, 32.4. $C_{17}H_{26}PI$ requires I, 32.7%), gave the *mercuri-iodide*, pale yellow needles, m. p. 82.5° (Found: I, 45.3; P, 23.5. $C_{17}H_{26}PI.HgI_2$ requires I, 45.2; P, 23.8%).

p-Isopropylphenyldi- β -methylallylphosphine.—Interaction of the Grignard reagent and *p*-isopropylphenyldichlorophosphine gave the phosphine (14 g.), b. p. 182.5°/19 mm., d_4^{25} 0.9279, n_D^{25} 1.5350 (Found: C, 77.9; H, 9.8; P, 11.8; M, 263. $C_{17}H_{25}P$ requires C, 78.4; H, 9.7; P, 11.9%; M, 260). Its *mercurichloride* was obtained in needles, m. p. 153° (Found: Cl, 13.4. $C_{17}H_{25}P.HgCl_2$ requires Cl, 13.3%).

p-Methoxyphenyldi- β -methylallylphosphine.—*p*-Methoxyphenyldichlorophosphine and di- β -methylallylmagnesium bromide reacted to give the phosphine (12 g.), b. p. 192°/20 mm., d_4^{25} 0.9948, n_D^{25} 1.5513 (Found: C, 72.3; H, 8.7. $C_{15}H_{21}OP$ requires C, 72.6; H, 8.6%). Its *mercurichloride* separated in cubes, m. p. 181° (Found: Cl, 13.8. $C_{15}H_{21}OP.HgCl_2$ requires Cl, 13.6%). *p-Methoxyphenylmethyldi- β -methylallylphosphonium iodide*, needles, m. p. 134.5°, from water (Found: I, 32.3. $C_{16}H_{24}OPI$ requires I, 32.5%) gave the *mercuri-iodide*, pale yellow prisms, m. p. 71° (Found: I, 45.0; Hg, 23.7. $C_{16}H_{24}OPI.HgI_2$ requires I, 45.1; Hg, 23.7%), and the *cadmi-iodide*, needles, m. p. 132° [Found: I, 44.2; Cd, 10.1. $(C_{16}H_{24}OPI)_2.CdI_2$ requires I, 44.3; Cd, 9.8%].

p-Bromophenyldi- β -methylallylphosphine.—Obtained from di- β -methylallylmagnesium bromide and *p*-bromophenyldichlorophosphine, this phosphine (14 g.) had b. p. 189°/18 mm., d_4^{25} 1.2094, n_D^{25} 1.5752 (Found: C, 56.7; H, 6.3; P, 10.3; M, 293. $C_{14}H_{19}BrP$ requires C, 56.6; H, 6.1; P, 10.4%; M, 297). The *mercurichloride* was obtained in cubes, m. p. 194° (Found: Cl, 12.4. $C_{14}H_{19}BrP.HgCl_2$ requires Cl, 12.5%). *p-Bromophenylmethyldi- β -methylallylphosphonium iodide*, cubes, m. p. 174°, from alcohol-ether (Found: I, 28.8. $C_{15}H_{21}BrPI$ requires I, 28.9%), yielded the *mercuri-iodide*, pale yellow needles, m. p. 67° (Found: I, 42.8; Hg, 22.4. $C_{15}H_{21}BrPI.HgI_2$ requires I, 42.6; Hg, 22.4%) and the *cadmi-iodide*, needles, m. p. 178° [Found: I, 40.8; Cd, 9.3. $(C_{15}H_{21}BrPI)_2.CdI_2$ requires I, 40.8; Cd, 9.0%]. On adding bromine to the phosphine in ether until a brown colour persisted, there was deposited an oil which solidified on being kept in a vacuum; on dissolving the solid in alcohol, adding water until turbidity developed, and allowing the mixture to stand, there formed crystals of *p-bromophenyldi-(β -dibromo- β -methylpropyl)phosphine oxide*, needles, m. p. 152°, from alcohol (Found: C, 26.6; H, 2.9; Br, 63.2; non-nuclear Br, 51.3. $C_{14}H_{19}OBr_2P$ requires C, 26.6; H, 2.9; Br, 63.1; non-nuclear Br, 50.5%).

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Preparation of the Arsines.—To the allyl or β -methylallyl Grignard reagent, prepared as already described, was added arsenic trichloride (6.8 c.c.) in ether (50 c.c.) or phenyldi-iodoarsine (51 g., obtained by the method of Steinkopf and Smie, *Ber.*, 1926, 59, 1461) in ether (200 c.c.). The isolation and purification of the arsine were also effected by redistillation under low pressure in carbon dioxide.

Phenyldiallylarsine.—This arsine (9 g.) was prepared by the interaction of allylmagnesium bromide and phenyldi-iodoarsine; it had b. p. $131^{\circ}/10$ mm. (Found: C, 61.3; H, 6.4; As, 31.3. $C_{11}H_{11}As$ requires C, 61.5; H, 6.5; As, 32.0%). It formed the *mercurichloride*, needles, m. p. 120° (Found: Cl, 13.8. $C_{11}H_{11}As.HgCl_2$ requires Cl, 14.0%).

Tri- β -methylallylarsine.—The compound (6 g.), obtained from β -methylallylmagnesium bromide and arsenic trichloride, had b. p. $114^{\circ}/15$ mm. (Found: C, 59.3; H, 8.7; As, 31.4. $C_{12}H_{14}As$ requires C, 60.0; H, 8.8; As, 31.2%). It yielded the *mercurichloride*, needles, m. p. $96-97^{\circ}$ (decomp.), from glacial acetic acid (Found: Cl, 14.2. $C_{12}H_{14}As.HgCl_2$ requires Cl, 13.9%), and *methyltri- β -methylallyl-arsonium iodide*, long rectangles, m. p. 129° (slight decomp.), from alcohol (Found: I, 33.0. $C_{12}H_{14}AsI$ requires I, 33.2%).

Phenyldi- β -methylallylarsine.—Interaction of the β -methylallyl Grignard reagent and phenyldi-iodoarsine gave the arsine (15 g.), b. p. $153^{\circ}/13$ mm., d_4^{25} 1.1200 (Found: C, 63.7; H, 7.5; As, 28.7. $C_{14}H_{19}As$ requires C, 64.1; H, 7.3; As, 28.6%). It formed *phenylmethyl-di- β -methylallylarsonium iodide*, needles, m. p. 163° (slight decomp.), from water (Found: I, 31.4. $C_{15}H_{21}AsI$ requires I, 31.4%).

Preparation of the Stannanes.—Triethylchlorotin, b. p. $209-210^{\circ}$, and diethyldichlorotin, m. p. 84° , were obtained by the methods of Kocheshkov (*J. Gen. Chem. Russia*, 1934, 4, 1359; 1935, 5, 211). **Tri-*n*-butylchlorotin** (40 g.) was prepared by heating (oil-bath) a mixture of tetra-*n*-butyltin (39 c.c.) and tin tetrachloride (4.6 c.c.) at 230° for 3 hours, and fractionating the product under low pressure; it had b. p. $172^{\circ}/25$ mm. (Found: Cl, 11.1. $C_{12}H_{27}SnCl_3$ requires Cl, 10.9%). **Di-*n*-butyldichlorotin** (20 g.) was obtained by heating a mixture of tetra-*n*-butyltin (16.5 c.c.) and tin tetrachloride (5.9 c.c.) for 3 hours at 240° , and recrystallising the product from light petroleum with cooling to -20° ; it formed plates, m. p. 40.5° (Found: Cl, 23.3. $C_8H_{19}SnCl_2$ requires Cl, 23.3%).

The chlorotin in benzene or ether was added to the allyl Grignard solution under hydrogen. After removal of the solvent and diallyl by distillation in carbon dioxide, the residue was dissolved in benzene (80 c.c.), the solution shaken with dilute sodium hydroxide solution to remove any traces of chloro-compound and then dried ($CaCl_2$), and the stannane isolated by distillation under low pressure in carbon dioxide.

Triethylallyltin.—This compound (21 g.) was prepared from the allyl Grignard solution and triethylchlorotin (30 g.) in benzene (90 c.c.), and had b. p. $76-77^{\circ}/10$ mm. (Found: C, 43.9; H, 8.3; Sn, 48.0. $C_6H_{13}Sn$ requires C, 43.8; H, 8.1; Sn, 48.1%).

Diethyldiallyltin.—Obtained by the action of the Grignard solution on diethyldichlorotin (16.8 g.) in benzene (60 c.c.), this compound (9 g.) had b. p. $99-100^{\circ}/17$ mm. (Found: C, 46.0; H, 7.7; Sn, 45.9. $C_{10}H_{20}Sn$ requires C, 46.3; H, 7.8; Sn, 45.9%).

Tri-*n*-butylallyltin.—The interaction of allylmagnesium bromide and tri-*n*-butylchlorotin (40 g.) in ether (120 c.c.) gave this compound as a liquid (30 g.), b. p. $155^{\circ}/17$ mm. (Found: C, 54.1; H, 9.8. $C_{18}H_{39}Sn$ requires C, 54.4; H, 9.8%).

Di-*n*-butyldiallyltin.—This compound (9.6 g.), prepared from the Grignard reagent and di-*n*-butyldichlorotin (19 g.) in ether (60 c.c.), had b. p. $145-146^{\circ}/17$ mm. (Found: C, 53.2; H, 9.1. $C_{14}H_{28}Sn$ requires C, 53.2; H, 9.0%).

The following derivatives were also prepared. **Ethyltrichlorotin** (6 g.) was obtained by refluxing tetraethyltin (7.9 c.c.) and tin tetrachloride (42 c.c.) for 24 hours and fractionating the product; it had b. p. $196-198^{\circ}$ (Found: Cl, 42.3. $C_6H_9SnCl_3$ requires Cl, 41.9%). After standing, a solution of 15 g. of allylstannonic acid (Found: Sn, 62.4. Calc. for $C_8H_9O_2Sn$: Sn, 61.5%) in a mixture of 50 c.c. of hydrobromic acid (d 1.5) and 50 c.c. of water deposited 40 g. of *allylpentabromostannic acid* (Found: Br, 71.2. $C_8H_7Br_5Sn$ requires Br, 71.2%); it separated in small, pale yellow cubes, soluble in water but not in organic solvents, and decomposed on heating.

The physical measurements here recorded were carried out with standardised apparatus, and all relevant corrections were applied. The yields given are not of crude, but of fully purified substance. Combustions were carried out by using lead chromate-copper oxide mixtures, determinations of phosphorus by the method of Davies and Davies (*J.*, 1931, 1207), of arsenic by that of Lewis and Davis (*J.*, 1939, 286), of tin by that of Gilman and King (*J. Amer. Chem. Soc.*, 1929, 51, 1213), and of mercury, cadmium, and iodine in complex salts by the method of Mannheim (*Annalen*, 1905, 341, 192).

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[Received, January 8th, 1947.]

274. Bromination of Dimethoxystilbenes.

By FELIX BERGMANN and HELENE JAPHÉ.

2 : 2'- and 3 : 3'-Dimethoxystilbene can be converted in a two-step process into symmetrical dibromodimethoxystilbenes. The 2 : 2'-compound is substituted in positions 5 and 5'.

In a recent publication (Bergmann and Schapiro, *J. Org. Chem.*, 1947, 12, 57) it was reported that 2-methoxystilbene undergoes nuclear bromination with such ease that in place of the expected dibromide there was obtained 5-bromo-2-methoxystilbene dibromide. We have now extended this observation to symmetrical dimethoxystilbenes.

Auwers (*Ber.*, 1903, 36, 1888), using excess of bromine, converted 4 : 4'-dimethoxystilbene into 3 : 5 : 3' : 5'-tetrabromo-4 : 4'-dimethoxystilbene dibromide. In this case, both positions

ortho to the methoxyl group are equivalent, whereas the *para* position is substituted by an olefinic chain. However, no disturbing effect is to be expected from this chain, as in all known cases the speed of addition of bromine to the central double bond of a stilbene is greater than that of nuclear substitution. The CHBr group is unlikely to exert any influence on this latter reaction, because Bance, Barber, and Woolman (*J.*, 1943, 1) observed the complete inertness of stilbene dibromide towards bromination in the ring. Therefore we assumed that in 2:2'-dimethoxystilbene dibromide the methoxy-groups would direct the attack of bromine exclusively. This was borne out by experiment.

After saturation of the double bond of 2:2'-dimethoxystilbene by bromine, substitution proceeded slowly, and although exactly 3 mols. of bromine were added, the reaction product was a mixture which could not be separated. It was, therefore, treated directly with potassium iodide. The mixture of bromostilbenes, so obtained, could be separated by fractional crystallisation into two substances of m. p. 214° and 130°, severally, which upon addition of 1 mol. of bromine yielded "dibromides" of m. p. 256° and 225° respectively. The compound of m. p. 214° is a dibromo-2:2'-dimethoxystilbene and was identified as the 5:5'-dibromoderivative by direct comparison with an authentic specimen (Ashley and Harris, *J.*, 1946, 567).

The substance of m. p. 130° contains only one bromine atom. That it was 5-bromo-2:2'-dimethoxystilbene was proved by its conversion *via* its dibromide into 5:5'-dibromo-2:2'-dimethoxystilbene dibromide. The reason for the incomplete conversion of 2:2'-dimethoxystilbene into the latter is to be found in the low reaction velocity. The monobromo-dibromide is sparingly soluble in chloroform, and if the bromine solution is added slowly, this compound has time to crystallise out, thus avoiding further bromination in the second ring. The preparation of the dibrominated bromide in nearly quantitative yield is, however, achieved easily, if excess bromine is added *at once* to a very dilute chloroform solution of 2:2'-dimethoxystilbene. This method thus presents a much easier route to 5:5'-dibromo-2:2'-dimethoxystilbene than the procedure of Ashley and Harris (*loc. cit.*).

3:3'-Dimethoxystilbene is converted smoothly into a dibromo-3:3'-dimethoxystilbene dibromide and hence into the corresponding stilbene; by analogy, these are deemed to be the 2:2'-dibromo-5:5'-dimethoxy-compounds, although we were unable to oxidise the stilbene to the expected 2-bromo-5-methoxybenzoic acid.

EXPERIMENTAL.

2:2'-Dimethoxystilbene.—By the procedure of Baumann and Fromm (*Ber.*, 1891, **24**, 1441), the required *o*-methoxythiobenzaldehyde is obtained mainly as a tough syrup and crystallizes only partly. However, the syrupy mass gave as good a yield (*ca.* 30%) upon thermal decomposition as did the crystalline portion. The crude stilbene was purified by distillation, b. p. 180–190°/0.5 mm., and then crystallized quickly upon trituration with methanol. It formed clusters of needles from butanol and prisms from toluene; m. p. 140°.

Bromination. (1) The stilbene (0.7 g.) was dissolved in chloroform (5 c.c.), and bromine (1.4 g.; 3 mols.) in the same solvent (5 c.c.) was added dropwise during 5 mins. The first third was decolorised instantaneously, then the speed of reaction slackened, and after addition of the second third of bromine a precipitate appeared. Decolorisation of the last third of bromine was very slow and was completed by warming on a water-bath. After the evolution of hydrogen bromide had ceased, the solvent was evaporated and the residue treated with methanol; yield 1.3 g., m. p. 218–220°. The product was not homogeneous, and crystallisation from xylene did not give a pure compound. It was, therefore, suspended in acetone (25 c.c.) and heated under reflux with sodium iodide (1 g.) for 3 hours. After evaporation of the solvent and addition of thiosulphate, a white substance was obtained. Upon recrystallisation from toluene, appeared first needles, then plates. They were separated by fractional crystallisation. The needles finally had m. p. 214° (Found: C, 48.4; H, 3.6. Calc. for $C_{16}H_{14}O_2Br_2$: C, 48.2; H, 3.5%) and were identified (mixed m. p.) as 5:5'-dibromo-2:2'-dimethoxystilbene described by Ashley and Harris (*loc. cit.*). The plates, recrystallised from isopropanol and then from light petroleum (b. p. 80°), formed glistening, elongated plates, m. p. 130° (Found: C, 60.0; H, 4.7. $C_{16}H_{14}O_2Br$ requires C, 60.2; H, 4.7%), of the *monobromostilbene*.

(2) 2:2'-Dimethoxystilbene (0.8 g.) was treated with bromine (2 mols.) in chloroform solution, and the product triturated with light petroleum. The 5-bromo-dibromide (1.6 g.; 100%) crystallised from toluene in colourless parallelepipeds with cut-off ends, m. p. 225° (Found: C, 39.8; H, 3.2. $C_{16}H_{14}O_2Br_3$ requires C, 40.1; H, 3.1%). It was identical with the compound formed by addition of bromine to the above monobromostilbene, into which it was converted by debromination with sodium iodide in acetone.

When the monobromostilbene was dissolved in chloroform and treated *at once* with excess of bromine, the dibromo-dibromide, m. p. 244° (see below), resulted.

(3) To 2:2'-dimethoxystilbene (6 g.; 1/40 mol.) in chloroform (50 c.c.) was added *at once* a solution of excess of bromine (20 g.; 5/40 mol.) in chloroform (50 c.c.), and the solution left overnight. The crude product (13.5 g.; 97%) had m. p. 244° and was difficult to recrystallise in greater amounts, because of decomposition. Small samples could be recrystallised from acetic anhydride, large volumes of xylene, or nitrobenzene. The products then showed different m. p.s; e.g., from xylene prisms of m. p. 245°, and from nitrobenzene of m. p. 256°. All these samples of 5:5'-dibromo-2:2'-dimethoxystilbene dibromide

showed identical analyses (Found : C, 34.2; H, 2.6. $C_{14}H_{14}O_2Br_4$ requires C, 34.4; H, 2.5%) and were quantitatively converted into the corresponding stilbene by debromination with sodium iodide or by the cuprous chloride-pyridine procedure of Bance *et al.* (*loc. cit.*).

3 : 3'-Dimethoxystilbene.—The desulphuration of *m*-methoxythiobenzaldehyde started at 200° and was completed by heating to 230° for 35 mins. The crude reaction product was mixed with an equal weight of copper-bronze and distilled in a vacuum; b. p. 180–182°/0.1 mm. The distillate crystallised spontaneously. From isopropanol it formed prismatic plates, m. p. 101°; yield 10%.

Bromination. To the stilbene (1.3 g.) in chloroform (10 c.c.) was added dropwise a solution of bromine (2.6 g.) in chloroform (8.3 c.c.). When addition was complete, 2 : 2'-dibromo-5 : 5'-dimethoxystilbene dibromide crystallised out. The solvent was evaporated, and the residue treated with ethanol; yield 2.7 g. (90%). From acetic anhydride the substance crystallises in hexagonal plates, m. p. 236° (Found : C, 34.6; H, 2.5. $C_{14}H_{14}O_2Br_4$ requires C, 34.4; H, 2.5%). Debromination with potassium iodide in acetone, as above, gave a 90% yield of 2 : 2'-dibromo-5 : 5'-dimethoxystilbene, which crystallised from toluene as prismatic rods, m. p. 154–155° (Found : C, 48.3; H, 3.7. $C_{14}H_{14}O_2Br_2$ requires C, 48.2; H, 3.5%).

The authors wish to thank Dr. J. N. Ashley, who carried out the comparison of 5 : 5'-dibromo-2 : 2'-dimethoxystilbene with an authentic specimen, prepared by him.

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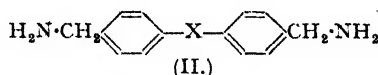
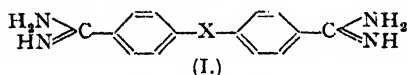
[Received, January 10th, 1947.]

275. Benzylamine Analogues of Chemotherapeutic Diamidines.

By ADRIEN ALBERT, JOHN A. MILLS, and RICHARD ROYER.

To help trace the origins of the outstanding chemotherapeutic properties of aromatic diamidines of type (I), the simpler bases of type (II) were synthesised for the first time.

THE researches of Ewins and his colleagues (*cf.* Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103) established that aromatic diamidines of type (I), especially *c*, *d*, *e*, and *f*, have outstanding antiparasitic properties against protozoa. It is not known (i) whether the anti-protozoal activity of these substances is derived largely from their having two well-ionized and mutually independent basic groups held at a distance from one another, or (ii) whether such activity depends specifically on the amidine group which may conceivably function by assisting adsorption, through the resonance of its ion, or by interfering with a similarly constituted metabolite in the parasite.



(a) X absent; (b) X = CH₂; (c) X = O;
(d) X = O·[CH₂]₃·O; (e) X = O·[CH₂]₆·O; (f) X = CH=CH.

At this stage we propose only to examine hypothesis (i). This cannot be tested simply by replacing each amidine group by an amino-group because the basic strength of the latter would be enormously lowered through interaction with the benzene ring (*cf.* aniline and methylamine, Table I), leading to an almost complete absence of kations in neutral solution. If, however, the amino-group is insulated from the aromatic ring by a methylene group, the base-weakening resonance is repressed and a high degree of ionization results (*cf.* benzylamine and methylamine, Table I). That the ionization of amidines is little affected by the presence of an aromatic substituent is now shown for the first time (Table I).

TABLE I.

Ionisation of certain bases under physiological conditions.

Compound.	pK _a , 20° (water).	Source of value,	% ionized pH 7.
Acetamidine	12.52	A	100
Benzamidine	11.6 (M/10)	B	100
Methylamine	10.76	C	100
Aniline	4.65	D	0.5
Benzylamine	9.4	E	99.5

- A. Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
B. Determined potentiometrically by Mr. R. Goldacre (for details of method, see Albert and Goldacre, *J.*, 1946, 706).
C. Britton and Williams, *J.*, 1935, 796.
D. Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
E. Carothers, Bickford, and Hurwitz, *ibid.*, 1927, **49**, 2908.

The preparation of the bisbenzylamine compounds (II, *a*—*f*) was accordingly undertaken to permit of biological comparison with the corresponding diamidines (I), in particular with *c* (Phenamidine), *d* (Propamidine), *e* (Pentamidine), and *f* (Stilbamidine).

The corresponding dinitriles were hydrogenated by the method of Schwoegler and Adkins (*J. Amer. Chem. Soc.*, 1939, **61**, 3499) for aliphatic amines, methanolic ammonia being used in the presence of Raney-nickel catalyst at 110° for 20 minutes under 1200 lb./sq. in. pressure. In this way were prepared *pp'*-bisaminomethyldiphenyl (II, *a*), *pp'*-bisaminomethyldiphenylmethane (II, *b*), characterized as its dibenzoyl derivative, *pp'*-bisaminomethyldiphenyl ether (II, *c*), 1 : 3-(*pp'*-bisaminomethyldiphenoxy)propane (II, *d*), 1 : 5-(*pp'*-bisaminomethyldiphenoxy)pentane (II, *e*), and *pp'*-bisaminomethylstilbene (II, *f*).

Before attempting the reduction of 4 : 4'-dicyanostilbene, it was confirmed that these conditions were not severe enough to reduce the double bond in *trans*-4 : 4'-diaminostilbene. The latter was made by reducing the mixture of dinitro- and dinitroso-stilbenes formed by the violent reaction of *p*-nitrotoluene and methanolic sodium hydroxide (Fischer and Hepp, *Ber.*, 1893, **26**, 2232). The mechanism of this reaction was investigated by Green, Davies, and Horsfall (*J.*, 1907, **91**, 2076), but no yields were given. As insufficient details exist in the literature for the safe and successful conduct of this reaction for preparative purposes, a detailed account is given in the experimental section.

The products (II, *a*—*f*) are white, water-insoluble solids which absorb carbon dioxide rapidly from the air but are stable in the form of their white, readily crystallising salts, of which the diacetates are more soluble than the dihydrochlorides and are to be preferred for biological work. That these substances possess the predicted basic strength may be inferred from the example quoted in Table II. This table also shows that, both here and in the diamidines, the two basic groups are too far apart for the ionization of the first to exert an adverse Coulombic effect on that of the second, such as is seen in trimethylenediamine (pK_a 9.8 and 7.0).

TABLE II.

Ionisation of certain diacid bases.

Compound.	pK_a values, 20° (50% ethanol).	Source of value.	Approx. % ionised in water at pH 7.
" Propamidine " (I, <i>d</i>)	11.6 & 10.8 (M/300)	B (see Table I)	100 & 100
<i>pp'</i> -Bisaminomethyldiphenyl- methane (II, <i>b</i>)	9.28 & 8.10 (M/160)		100 & 97

Von Braun (*Ber.*, 1937, **70**, 979) claimed to have produced (II, *a*) by the action of liquid ammonia on *pp'*-bisbromomethyldiphenyl; it is possible that his material was contaminated by secondary amines.

Note added in Proof.—Compounds (I, *c*—*f*) and (II, *a*—*f*) were kindly compared by Mr. L. G. Goodwin in experimental animal tests against *Trypanosoma rhodesiense*, *T. congolense*, *Plasmodium gallinaceum*, *Leishmania donovani*, and *Entamoeba histolytica*. No activity was shown by any Type (II) compound. We are also grateful to Prof. S. D. Rubbo for testing the same series, *in vitro*, against *Cl. welchii*, *Strept. pyog.*, *Staph. aur.*, *B. coli*, and *B. Proteus*. Only (I, *d* and *e*) showed outstanding activity.

Thus, unless it can be shown that these organisms possess an enzyme specifically destroying Type (II) compounds, hypothesis (i) is no longer tenable.

EXPERIMENTAL.

[The microanalysis of bisaminomethyldiphenyl and its hydrochloride were carried out by one of us (J. A. M.); the remainder were done by Miss J. Fildes, who is hereby thanked.]

General.—The dinitrile (15 g.), Raney-nickel catalyst (*ca.* 5 ml. of sludge), and methanolic ammonia saturated at 0° (150 ml.) were placed in a chilled-steel hydrogenation bomb (unlined) with two $\frac{1}{8}$ in. steel balls. These proportions allow about 7 mols. of ammonia, per cyano-group. Hydrogen was admitted at an initial pressure of 1300 lb./sq. in., and maintained at about 1200 lb. whilst the bomb was heated to 110° in 30 minutes with shaking. Uptake of hydrogen began at about 70°. It was rapid and approximately that required by theory. The autoclave was allowed to cool, and then chilled in ice. It was opened, and the contents filtered quickly with the assistance of some methanolic ammonia, in which the amines dissolve much better than in methanol. Carbon dioxide was excluded as much as possible from this and subsequent operations. The solvent was recovered by using a bath at 140° and applying a vacuum towards the end. The amines (crude yields about 90%) solidified on cooling and sometimes contained colloidal nickel hydroxide which caused foaming when the solids were distilled.

pp'-Bisaminomethyldiphenyl (II, *a*).—This was purified by distillation (*b. p.* 180°/0.5 mm.) and recrystallisation from 10 parts of toluene. The yield of pure material was 80%. A slightly under-

hydrogenated batch supersaturated badly. The substance is soluble in hot alcohol, benzene, and ethyl acetate, and in cold pyridine (Found: C, 79.5; H, 7.5; N, 13.3. Calc. for $C_{14}H_{15}N_3$: C, 79.2; H, 7.6; N, 13.2%). The compound and its derivatives had the following m. ps. (values of v. Braun, *loc. cit.*, in parenthesis): base, 144–145° (135°); picrate, 232–235° (decomp.) (222°); dibenzoyl derivative, 249–250° (243°); diacetyl derivative, 281–283° (272°). The dihydrochloride was formed by crystallisation from hot dilute hydrochloric acid. It is soluble in about 100 parts of cold water and readily precipitated by extra chloride ions (Found: C, 59.15; H, 6.3; Cl, 24.7. $C_{14}H_{15}N_3Cl_2$ requires C, 58.95; H, 6.4; Cl, 24.9%). The crystals developed a blue tint on exposure to sunlight.

pp'-Bisaminomethylidiphenylmethane (II, b).—This was purified by distillation at 0.5 mm., followed by dissolution in 5 parts of boiling benzene and treatment with 5 parts of light petroleum (b. p. 60–90°). The white crystals, m. p. 90° (80% yield), were dried in a vacuum over shredded paraffin. The compound is very soluble in alcohol without gradient, sparingly soluble in ether (Found: C, 79.4; H, 7.9; N, 12.2. $C_{15}H_{16}N_2$ requires C, 79.6; H, 8.0; N, 12.4%). The dihydrochloride (m. p. over 350°) is exceptional in this series in that it is difficult to precipitate with chloride ions; it is almost insoluble in alcohol and unaffected by light. The dibenzoyl derivative was prepared with benzoyl chloride in 10 volumes of pyridine (yield 90%) as white crystals from chlorobenzene, m. p. 224° (230° corr.), sparingly soluble in benzene, acetone, and alcohol (Found: N, 6.4. $C_{22}H_{20}O_2N_2$ requires N, 6.45%).

pp'-Bisaminomethylidiphenyl ether (II, c).—This was distilled (b. p. 186°/0.3 mm.), giving crystals (70% recovery) which began to melt at 56° and were completely molten at 77° (? double m. p.). The product was readily soluble in ethyl and amyl alcohols and in boiling toluene or acetone with gradient; only slightly soluble in ether and in light petroleum (Found: C, 73.0; H, 7.1; N, 12.2. $C_{14}H_{14}ON_2$ requires C, 73.6; H, 7.1; N, 12.3%). The dihydrochloride does not melt below 360°. The diacetate (m. p. 156°, anhydrous) was formed by dissolving the base in 8*N*-acetic acid at 50°, precipitating with acetone, and drying at 110°. It was readily soluble in cold water and hot ethanol.

1:3-(*pp'*-Bisaminomethylidiphenyloxy)propane (II, d).—This was purified by distillation (b. p. 242°/0.5 mm.) and then recrystallised from alcohol, m. p. 90–91° (70% yield). It is sparingly soluble in boiling benzene; moderately so in boiling acetone. The dihydrochloride is sparingly soluble in cold water and readily soluble in hot water; it sinters at ca. 290° but does not melt below 360°. The diacetate, m. p. 178°, prepared as above, is readily soluble in cold water, moderately in boiling alcohol, and insoluble in acetone (Found: C, 62.0; H, 7.4; N, 6.85. $C_{17}H_{22}O_2N_2$, $2C_2H_5O_2$ requires C, 62.0; H, 7.4; N, 6.9%).

1:5-(*pp'*-Bisaminomethylidiphenyloxy)pentane (II, e).—This was purified through the acetate without previous distillation. The base (70% yield), m. p. 74–75°, from aqueous ethanol, is readily soluble in pyridine and in methanol and has good gradients in toluene and chlorobenzene. It is very slightly soluble in ether and in light petroleum. The dihydrochloride is soluble in cold water and insoluble in ethanol and acetone. It sinters at ca. 270° but does not melt below 360°. The diacetate, m. p. 161°, is very soluble in water, moderately in cold and readily in boiling ethanol, and insoluble in acetone (Found: C, 63.4; H, 7.8; N, 6.4. $C_{19}H_{26}O_2N_2$, $2C_2H_5O_2$ requires C, 63.55; H, 7.9; N, 6.45%).

pp'-Bisaminomethylstilbene (II, f).—This compound was purified by recrystallisation first from chlorobenzene and then from ethanol, giving crystals, m. p. 210–211° (decomp.) on rapid heating (yield 75%). They are soluble in about 27 parts of boiling ethanol, moderately soluble in boiling benzene or pyridine (with gradient), and almost insoluble in acetone, ether, or light petroleum (Found: C, 80.6; H, 7.6; N, 11.7. $C_{14}H_{15}N_2$ requires C, 80.6; H, 7.6; N, 11.8%). The dihydrochloride is moderately soluble in boiling water (with gradient) and insoluble in alcohol or acetone. The diacetate, m. p. 206–207°, solidifies at 210° and melts again at 255° (approx.) and is readily soluble in water, slightly soluble in boiling alcohol, and insoluble in acetone.

trans-pp'-Diaminostilbene.—A three-neck flask (capacity 1 l.) was fitted with an efficient mechanical stirrer, a 24-in. water-cooled bulb condenser, and a cork containing a thermometer, the bulb of which was pushed down below the 250 ml. level. The operation was conducted under a good hood.

Sodium hydroxide sticks (125 g.) were broken into coarse grit and refluxed in the flask with methanol (500 ml.) until dissolved (about 90 minutes), heat being supplied by a glycerol-bath at 100°. The flame was extinguished, and the thermometer momentarily withdrawn while molten *p*-nitrotoluene (50 g.) was rapidly added. After 30 seconds a violent reaction set in, the temperature rising to 105° and falling back to 90° when the condensed methanol returned to the flask. The flask contents became deep red. The glycerol-bath was then heated for ½ hour to keep the flask contents at 100°. The thermometer was then withdrawn, and a condenser, arranged for distillation, inserted. Concentrated hydrochloric acid (1 equiv.; 300 ml. of 39% w/v) was added down the upright condenser during 15 minutes with rapid stirring. The bath was then maintained at 120° until 400 ml. of methanol, altogether, had been collected. The product consisted of a mixture of dinitrodibenzyl, dinitrostilbene, and (mainly) dinitrostilbene. These substances were separated by Fischer and Hepp, but it was found more economical to reduce them together, *in situ*, taking advantage of the relative insolubility of diaminostilbene salts.

The temperature of the bath was lowered to 100°, and a solution of stannous chloride crystals (330 g.; 4 mols. per mol. of nitrotoluene) in concentrated hydrochloric acid (330 ml.), warmed to 80°, was added down the upright condenser during 15 minutes. Stirring and heating at 100° (bath temp.) were continued for 2 hours. The flask was then cooled and kept in ice for 2 days.

The precipitate of sodium chloride and diaminostilbene stannichloride was filtered off, pressed well, and extracted successively with 500, 200, and 50 ml. of boiling water, leaving about 1 lb. of sludge. The combined filtrates were boiled and treated with sodium hydroxide (ca. 350 ml. of 5*N*) until Orange-II paper was reddened. The mixture was heated for ½ hour on the boiling water-bath and again adjusted to reddish Orange-II. The precipitate was filtered hot, pressed, and washed until the filtrate ceased to redden phenolphthalein. The cake was dissolved in the minimum (ca. 300 ml.) of boiling *N*-hydrochloric acid, 75 ml. of 10*N*-hydrochloric acid were then added, and the whole refrigerated overnight. Next day the diaminostilbene hydrochloride was filtered off, dissolved in boiling water (150 ml.) containing 10*N*-hydrochloric acid (1 ml.), and treated with sodium hydroxide, as above. The cake was collected, pressed hard, washed well, and dried at 120°. The yield was 17.0 g. (45%) of orange powder, m. p. 214°.

This was purified by boiling with 20 parts of chlorobenzene, filtering hot, and cooling in ice for a day (85% recovery; m. p. 225–226°).

Finally, recrystallisation from dilute alcohol removed a trace of orange impurity and gave minute, almost colourless crystals, m. p. 227–228° equal to the highest uncorrected m. p.s in the literature (Calvin and Buckles, *J. Amer. Chem. Soc.*, 1940, **62**, 3324; Klinge, *Ber.*, 1883, **16**, 943).

The authors wish to thank Professors J. C. Earl and A. K. Macbeth for their interest in this work, and Dr. A. J. Ewins for supplying the dinitriles. This work was supported by the National Health and Medical Research Council, the Commonwealth Research Fund, and the Wellcome Foundation.

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[Received, January 13th, 1947.]

276. *The Crystal Structure of Ammonium Nitrate III, and Atomic Scattering Factors in Ionic Crystals.*

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The crystal structure of ammonium nitrate III has been redetermined in the light of revised optical and X-ray evidence.

IN the course of an investigation into the conditions of stability of ammonium nitrate III, the form normally stable from 32·3° to 84·2°, we measured the series of single-crystal rotation and oscillation photographs which we obtained, and compared our data with those of Hendricks, Posnjak, and Kracek (*J. Amer. Chem. Soc.*, 1932, **54**, 2776). Although there is general agreement between their observations and ours, there are certain marked discrepancies [see information in Tables II and III concerning the planes (002) and (004), (101), and (200)]. Moreover, there are frequently wide discrepancies between their observed and calculated intensities, as, for example, for the planes observed to have "moderate" intensities.

We are unable to account for the observational discrepancies, but for the rest, it seems possible that the authors were aware of the optical data which Hendricks, Deming, and Jefferson published later (*Z. Krist.*, 1933, **85**, 145) and, believing them to be correct, proposed a structure in conformation with them. They say that their agreement between observed and calculated intensities is only moderate. A difficulty in trying to explain these discrepancies is that although the authors state that the interfacial angles between the needle zone faces is 90° 0' (faces therefore $a\{100\}$ and $b\{010\}$) they quote no data derived directly from rotation, oscillation, or Weissenberg photographs about the a - or b -axes apart from the intensities of $\{001\}$ which we consider erroneous and for which they fail to record calculated intensities. We therefore decided to redetermine the structure.

Since ammonium nitrate III is stable only above 32°, all manipulations of the crystals had to be carried out above this temperature. The specimens used were grown from aqueous-alcoholic solution in a thermostatic hot-air chamber at 50°, and selected and mounted while still in the chamber. They were then rapidly transferred to the goniometer arcs while a stream of hot air at *ca.* 42° was allowed to flow over crystal and arcs alike. Optical goniometry revealed that the crystals, which were long needles, usually had only the four prism faces of the $\{110\}$ form present, the angle $(110):(1\bar{1}0)$ being 94°. There is probably no significance in this difference of habit between our crystals and those of Hendricks *et al.*

After the camera had been placed in position, hot air was introduced into it by a wide tube inserted through the lid and reaching down to near the level of the crystal, a thermometer being present in the air stream to ensure maintenance of a sufficiently high temperature (*ca.* 42°). The X-radiation employed was from the copper target of a Shearer tube with a nickel-foil filter. The following axes were measured: $a = 7\cdot14$, $b = 7\cdot65$, $c = 5\cdot83$ Å. These compare satisfactorily with the results of Hendricks *et al.*, *viz.*, $a = 7\cdot06$, $b = 7\cdot66$, $c = 5\cdot80$ Å. Examination of oscillation photographs about the a , b , and c axes revealed $\{0kl\}$ present only when k is even, $\{h0l\}$ present only when $h + l$ is even, $\{h\bar{h}0\}$ and $\{h\bar{h}l\}$ present in all orders. These extinctions are consistent with the space-group $Pbnm$ (V_h^{16}) assumed by the American investigators although Pbn (C_{2h}^3) is also possible. For preliminary calculations the space-group of higher symmetry $Pbnm$ was assumed.

The structure factors for planes of the $\{h\bar{h}0\}$ zone are the same for both space-groups and, as is shown later, the atomic positions were deduced by constructing a Fourier projection on (001). Since it was impossible to carry out work with heated crystals on the Weissenberg

instrument available, visual estimates of intensities had to be made from rotation and oscillation photographs, with consequent limitations of accuracy. It was found possible, using the atomic positions definitely located by the Fourier synthesis, to postulate a structure based on the symmetry elements of *Pbnm*, giving satisfactory agreement between observed and calculated intensities within the limits of accuracy of the work. In addition, the packing of the atoms in the unit cell is such that there is little possibility of changes in the relative positions indicated if on the one hand the projection on (001) is to be maintained while on the other the space-group is to be altered to *Pbn*; any such changes would increase the range of $\text{NH}_4 \dots \text{O}$ distances observed on the structure. Thus we consider that the choice of the space-group of higher symmetry, *Pbnm*, is justified.

In this space-group, then, eight asymmetric units are required, four being mirror images of the others, but as only four NH_4NO_3 units, *i.e.*, four NH_4^+ and four NO_3^- ions, are present, these must possess two-fold symmetry; since the space-group does not involve axes of rotation, the ions are restricted to central or planar symmetry. Both these types need to be considered for, though neither the tetrahedral NH_4^+ nor the planar NO_3^- group can have a centre of inversion when "at rest", in ammonium nitrate I, the form stable from 125° to the melting point at 169.5° , there is only one ion of each species in a cubic cell and therefore each must be rotating in a way which enables it to simulate cubic symmetry. In ammonium nitrate III rotation of the NH_4^+ and NO_3^- could confer on them pseudo-central symmetry. On the other hand, (a) the latter modification is stable at considerably lower temperatures and its ions are therefore less likely to be rotating in the solid state, and (b) the number of ions present is the minimum required if they are planar and at rest. We decided, therefore, to begin by placing the nitrate ions on the symmetry planes, but in view of the fact that the ammonium ions are more nearly spherical and therefore more readily capable of free rotation, we decided to consider their location at centres of inversion and on planes of symmetry in turn. In the latter case the co-ordinates of the ammoniacal nitrogen are :

$$(a) \ u_A, v_A, \frac{1}{4}; \ u_A, \bar{v}_A, \frac{3}{4}; \ \frac{1}{2} - u_A, \frac{1}{2} + v_A, \frac{1}{4}; \ \frac{1}{2} + u_A, \frac{1}{2} - v_A, \frac{3}{4}.$$

In the former they may be either :

$$(b) \ 0, 0, 0; \ 0, 0, \frac{1}{2}; \ \frac{1}{2}, \frac{1}{2}, 0; \ \frac{1}{2}, \frac{1}{2}, \frac{1}{2}, \text{ or } (c) \ \frac{1}{2}, 0, 0; \ \frac{1}{2}, 0, \frac{1}{2}; \ 0, \frac{1}{2}, 0; \ 0, \frac{1}{2}, \frac{1}{2}.$$

For the nitrate ions two dispositions on the symmetry planes of the crystal are possible, *viz.*, so that all four atoms of each ion are on the (same) symmetry plane or so that the nitrogen and one oxygen are on the plane, the other oxygens being above and below this. In the first case pronounced negative optical birefringence would occur, the minimum refractive index α being perpendicular to the symmetry planes, *i.e.*, parallel to the *c*-axis (cf. potassium nitrate and aragonite; Bragg, "Atomic Structure of Minerals", Oxford Univ. Press, 1937, pp. 119 *et seq.*). In the second, γ , the greatest refractive index, would be parallel to *c*. In fact, γ is parallel to *c*, so that the second possibility is the correct one; since the optic axial angle is high ($2V \approx 90^\circ$) it follows that the plane of the ion must be quite oblique to both the *a* and the *b* axis.

The atomic co-ordinates of N and one O of the NO_3^- must therefore be as in (a) above but with parameters u_N, v_N and u_O, v_O . The other oxygens are in general (*i.e.*, eight-fold) positions :

$$(d) \ x, y, z; \ \bar{x}, \bar{y}, \frac{1}{2} + z; \ \frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z; \ \frac{1}{2} + x, \frac{1}{2} - y, \bar{z}; \\ x, y, \frac{1}{2} - z; \ \bar{x}, \bar{y}, \bar{z}; \ \frac{1}{2} - x, \frac{1}{2} + y, z; \ \frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z.$$

To locate the various atoms, we first considered the orders of (001) since they involve only the *z*-co-ordinates. For those the structure factor F_{00l} is :

$$F_{00l} = 8f(\text{O}) \cos 2\pi lz + 4f(\text{O}) \cos 2\pi \frac{l}{4} + 4f(\text{N}) \cos 2\pi \frac{l}{4} + 4f(\text{A}) \cos 2\pi \frac{l}{4},$$

$$\text{or} \quad F_{00l} = 8f(\text{O}) \cos 2\pi lz + 4f(\text{O}) \cos 2\pi \frac{l}{4} + 4f(\text{N}) \cos 2\pi \frac{l}{4} + 4f(\text{A}) \cos 2\pi \frac{l}{2}$$

according as the ammonium ion is situated on the symmetry plane or at a symmetry centre; $f(\text{O})$, $f(\text{N})$ and $f(\text{A})$ are the atomic scattering factors of oxygen, nitrate nitrogen, and ammonium respectively. Hendricks, Posnjak, and Kracek "assumed that $f(\text{A})$ for Cu-K radiation is

approximately the same as determined for Mo-*K* radiation diffracted from NH_4Cl (Wyckoff and Armstrong, *Z. Krist.*, 1929, **72**, 319), that $f(\text{O})$ is the same as for oxygen in nickel oxide (Cu-*K* radiation) (Wyckoff, *Physical Rev.*, 1930, **35**, 583; "Structure of Crystals", 2nd Edn., 1931, p. 100), and that $f(\text{N}) = 0.35 f(\text{O})$ independent of $\sin \theta/\lambda$. It is thus implied that, so far as the diffraction of *X*-rays is concerned, the nitrate ion approximates to a N^{5+} ion surrounded by three O^{2-} ions. In view of the completed *L* shells of nitrogen and oxygen in nitrate ions as formulated by chemists, we have preferred to regard the *f* values of these atoms as the same, with $f_0(\text{N}) = f_0(\text{O}) = 8$, f_0 being the value of *f* when $\theta = 0$. Of the various theoretical arguments in support of this view, we quote only two. It is well known that the polarising power of a cation increases with increasing charge and decreasing radius. Since the "radii" of N^{5+} and, say, Li^+ are quoted by, e.g., Pauling ("Nature of the Chemical Bond", 2nd Edn., p. 346) as 0.11 and 0.60 Å., respectively, it follows that the polarising power of the N^{5+} will be so great as to lead to N-O bonds which are essentially covalent. Secondly, the uniformity of structure of the nitrate ion as a planar equilateral triangle in which the central nitrogen has no tendency to be surrounded by more than three oxygens or other "anions", shows that the N-O bonds are directed in space and therefore are covalent, not electrovalent.

Using, then, these atomic scattering factors, we found that if the NH_4^+ ion is on the mirror plane *z* must have a value of between 0.06 and 0.07 in order to account for the observed relative intensities of (002), (004) and (006); *z* was selected as 0.06, equivalent to a distance of about 2.21 Å. for O . . . O in the nitrate ion, or 1.27 Å. for N . . . O, which latter value lies between the measurement of 1.21 Å. made by Elliott (*J. Amer. Chem. Soc.*, 1937, **59**, 1380) for the nitrate ion in sodium nitrate, and the value of 1.31 Å. calculated by Pauling on the basis of one double bond resonating between the three positions. If the ammonium ion was placed at a symmetry centre no such satisfactory relative intensities could be calculated.

We next drew, on scaled diagrams of the (001) plane, the traces of various particularly strong and particularly weak $\{hk0\}$ planes (excluding space-group halvings). On examining the resulting diagram with the assistance of a scale model of the nitrate ion (edge = O . . . O proportional to 2.21 Å.), arranged so that one O . . . O direction was perpendicular to the diagram, tentative positions for the atoms of this ion were obtained which permitted a reasonable location of the NH_4^+ ion on the symmetry plane. From these we calculated, after some slight adjustments, structure factors which were in approximate agreement with our qualitative estimates of intensity. In an endeavour to refine the structure we then made by visual estimation numerical assays of the intensities of as many as possible of the $\{hk0\}$ planes from rotation and oscillation photographs and constructed a Fourier projection on (001).

This projection proved far from satisfactory because, while indicating unequivocally the two oxygens in the general positions (*d*), it left considerable doubt as to the placing of the ammonium ion and the third oxygen on the reflection planes. One of these was revealed as a definite peak in the landscape but the other only as an upland region. According to whether and where the ammonium or oxygen is placed in this upland region three alternative structures are obtained which give *F* values for the $\{hk0\}$ planes of roughly the same magnitude as those estimated visually. However, by trial and error methods the ammonium ion was eventually placed in this region in a position which led to satisfactory agreement with the intensities of reflections over all three principal zones as well as for the $\{hkl\}$ planes. The nitrate nitrogen was suitably located on the line joining the "special" and "general" oxygens in the projection. In view of the large changes in structure amplitude brought about in certain planes by movements of the atoms of less than one-hundredth of the cell edge, and the impossibility of testing all the combinations of atomic positions within the tolerances allowed by the Fourier synthesis, the agreement between observed and calculated intensities is as good as can be expected.

TABLE I.

Atomic co-ordinates.

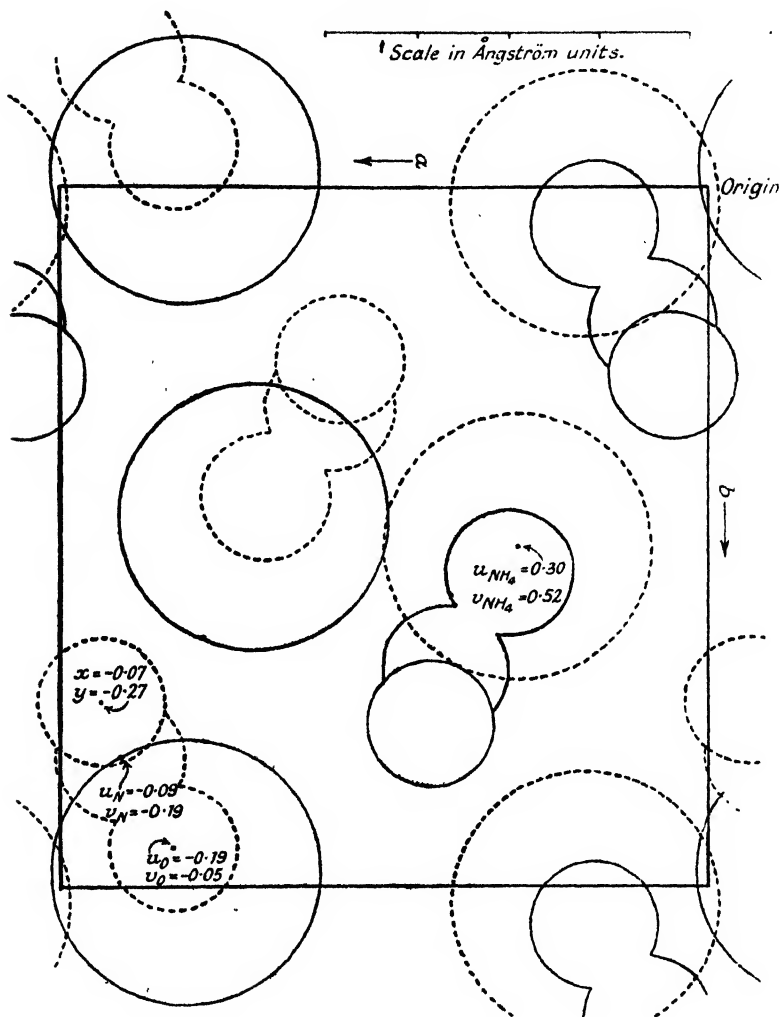
<i>x</i> = 0.05–0.06	<i>y</i> = 0.17–0.175–0.18	<i>z</i> = 0.06–0.07
<i>x_N</i> = 0.13–0.14	<i>v_N</i> = 0.14–0.145–0.15	<i>w_N</i> = 0.25
<i>x_O</i> = 0.30–0.29	<i>v_O</i> = 0.08–0.085–0.09	<i>w_O</i> = 0.25
<i>x_{NH₄}</i> = 0.30–0.32	<i>v_{NH₄}</i> = –0.02 to –0.03	<i>w_{NH₄}</i> = –0.25

Table I gives the limits within which we consider the parameters of the various atoms to lie, the figures in *italics* being those used in calculating the structure factors and intensities of Tables II, III, and IV.

Since the crystals were thin needles of nearly square cross-section, it was considered unnecessary to apply absorption corrections to the observed intensities of the $\{h k 0\}$ planes. They have, however, been applied to those of the other prism zones, though not to the $\{h k l\}$ planes, calculations of which were made rather as a final check.

In Table II are given first the observed intensities of the planes of the $\{h k 0\}$ zone. Then in col. 3 are recorded the structure factors calculated from the final ionic model, the four atoms

FIG. 1.

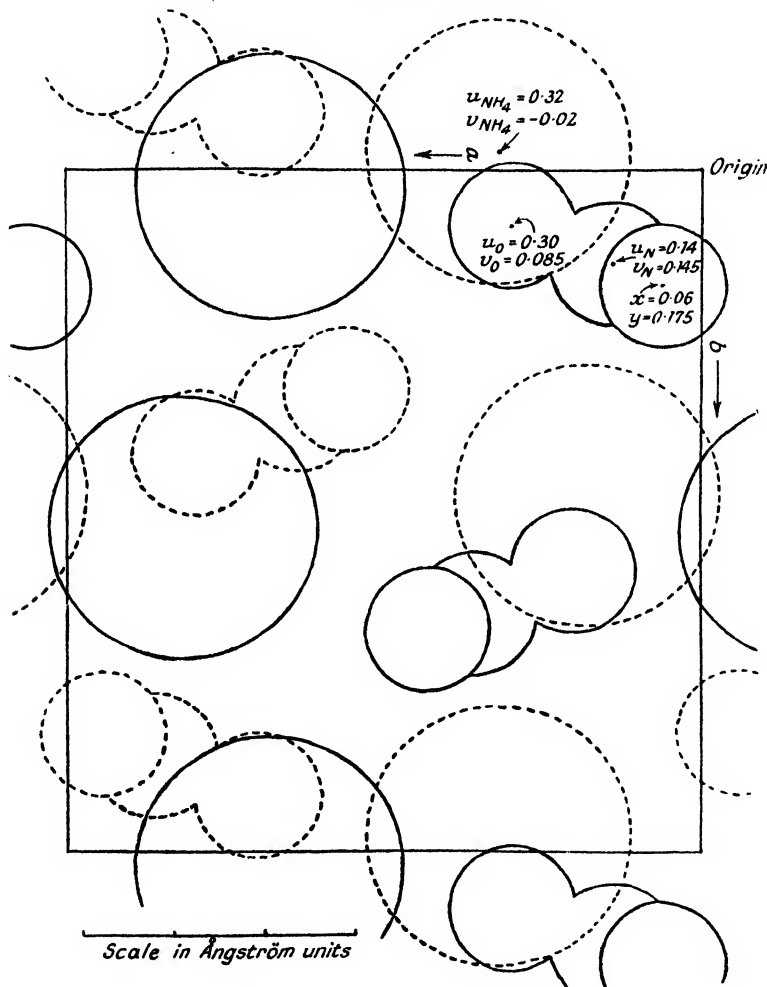


of the nitrate ion all being supposed to have the same atomic scattering factors with $f_0(O) = f_0(N) = 8$. Col. 4 gives the factor $L = (1 + \cos^2 2\theta) \sin 2\theta$ by which F^2 is converted into the intensity I , recorded in col. 5. Cols. 6 and 7 record the intensities observed and calculated by Hendricks *et al.* Table III contains the absorption corrections where applied; these were calculated from the lengths of the paths of the X-ray beam through the crystals and the mass absorption coefficients recorded in the "International Tables for the Determination of Crystal Structures," 1933, Vol. II, p. 577. Apart from this, Tables III and IV will be readily understood by comparison with Table II.

It will be seen that our observed and calculated results are in better agreement than those of Hendricks, Posnjak, and Kracek. The principle difference between the two structures is in the disposition of the nitrate ions, which in our model (Fig. 1) are more nearly parallel to the

a- than to the *b*-axis, the converse being the case with the structure reported by the Americans (Fig. 2). Our proposal would therefore lead to refractive indices $\alpha//b$, $\beta//a$, $\gamma//c$. The measured values as recorded by Hendricks, Deming, and Jefferson (*Z. Krist.*, 1933, 85, 145) are $\alpha = 1.463/a$, $\beta = 1.543/b$, and $\gamma = 1.600/c$. Our own measurements, carried out on mounted crystals of known orientation (as determined by X-rays) agree with these numerically, but we find $a//b$ and $\beta//a$. In view of the fact that the crystals are long needles with their needle zone

FIG. 2.



FIGS. 1 and 2.—Fig. 1 represents the unit cell of ammonium nitrate III deduced in this investigation, projected parallel to the *c*-axis; Fig. 2 is a similar projection of the structure of Hendricks, Posnjak, and Kracek. The unbroken and the dotted circles represent atoms located on or about reflection planes at $c = \frac{1}{2}$ and $\frac{3}{4}$, respectively. The large circles represent ammonium ions (Pauling's radius 1.48 Å.), while the groups of small circles represent the nitrate ions, and oxygens in the general positions being superimposed one on another in the projection. The radii of oxygen and nitrogen are taken as Pauling's covalent radii (0.66 Å. and 0.70 Å., respectively).

faces at or nearly at right angles, it is not surprising that the vibration directions of the fast and medium rays should have been wrongly identified. Thus the revised optical properties support our proposed ionic arrangement. In our structure the NH_4^+ ions are distant 2.7–3.2 Å. from their nearest oxygen neighbours, while in theirs the mean of nine such distances ranging from 2.75 to 3.13 Å. is 2.95 Å.

TABLE II.

hko.	Intensity,		F, calc.	L.	Intensity :		
	obs.	num.			G. & W.,	H., P., & K.,	
					calc.	obs.	calc.
200	500	—	10	4.5	450	vw	8
400	130	—	12	1.7	250	vw	8
600	—	—	10	1	100	vw	—
020	0—30	—	7	4	200	vw	1
040	1300	—	14	2	400	m	660
060	800	—	30	1	900	w	—
110	1000	—	15	6.5	1450	m	550
210	8000	—	44	3.75	7000	vvs	3000
310	2600	—	38	2.5	3600	mms	10
410	1800	—	35	1.7	1750	s	400
510	800	—	31	1.25	1200	m	—
610	—	—	3	1	10	—	—
120	5000	—	45	4	8000	ms	370
220	10,000	—	44	3	6000	s	500
320	1300	—	28	2	1600	m	90
420	260	—	1	1.5	—	w	50
520	400	—	15	1.25	250	w	—
130	10,000	—	60	2.75	9900	s	270
230	500	—	4	2.2	40	mw	140
330	500	—	20	1.7	700	vw	80
430	130	—	—	1.35	—	w	—
530	—	—	3	—	10	—	—
140	250	—	14	1.8	350	a	200
240	130	—	10	1.7	170	a	15
340	2300	—	31	1.4	1300	mms	—
440	130	—	4	1.1	20	—	—
540	—	—	8	1	64	—	—
150	800	—	15	1.5	350	—	—
250	260	—	21	1.3	500	—	—
350	500	—	14	1.2	270	—	—
450	—	—	3	1	10	—	—
160	—	—	15	—	—	—	—
260	—	—	10	—	—	—	—
360	—	—	5	—	—	—	—

TABLE III.

h0l or 0k.	Intensity,		F, calc.	Abs.,		Intensity, calc.		
	obs.			corr.	L.	G. & W.	H., P., & K.	
101	ms	22	2	2	5	1125	4000	—
103	vw—a	4	4	1.8	1.8	16	—	—
105	w	11	11	2.2	1.0	50	—	—
202	s	58	58	2.3	2.45	4000	750	—
204	m	24	24	2.3	1.2	310	—	—
206	w	8	8	?	1.2	?	—	—
301	vw	14	14	12.5	2.4	40	200	—
303	mw	21	21	3.3	1.5	200	160	—
305	vw	16	16	?	1.0	?	—	—
402	a	10	10	10	1.4	14	3	—
404	a	8	8	?	1	?	—	—
406	a	7	10	10	1.2	5	—	—
501	w	8	8	3	1.2	25	—	—
503	vw	20	20	?	1	?	—	—
505	vw	6	6	?	1.5	?	—	—
002	s	37	37	—	3.4	4630	—	—
004	m	31	31	—	1.3	1250	—	—
006	w	23	23	—	1.1	580	—	—
021	s	54	54	3.3	3.7	4000	70	—
023	vw	11	11	2.1	1.7	90	—	—
025	mw	32	32	?	1	?	—	—
022	s	54	54	2.1	2.5	3450	1250	—
024	mw	23	23	2.1	1.2	300	—	—
026	a	9	9	?	1.1	?	—	—
041	a	6	6	4.5	1.8	15	20	—
043	mw	35	35	4	1.25	375	10	—
045	a	4	4	?	1.1	?	—	—
042	a	8	8	4	1.4	20	2	—
044	a	1	1	4	1	0	—	—
046	a	3	3	?	1.7	?	—	—

TABLE IV.
I, calc.

I, F, H., P.,					I, F, H., P.,						
hkl.	obs.	calc.	L.	G. & W.	& K.	hkl.	obs.	calc.	L.	G. & W.	& K.
111	s	23	4.7	2500	1300	151	w	22	—	—	—
211	s	32	3.5	3500	15	251	w	20	1.2	480	—
311	vw	3.5	2	20	0	112	s	23	2.9	1550	400
411	w	8	1.5	100	7	212	vw	5	2.4	60	80
511	w	13	1.2	200	—	312	mw	20	1.7	680	280
121	ms	25	3.5	2200	240	412	mw	17	1.3	380	140
221	w	8	2.6	170	30	122	m	16	2.4	700	280
321	mw	7	1.9	100	130	222	mw	11	2	250	65
421	a	9	1.4	110	2	322	mw	16	1.5	380	15
521	vw	8	1.1	70	—	422	w	3	1.4	13	3
131	mw	8	2.4	150	100	132	a	3	1.8	16	10
231	w	5	2	50	5	232	w	7	1.6	80	100
331	vw	10	1.6	160	37	332	ms	34	1.4	1500	0
431	mw	23	1.3	650	—	432	vw	6	1.1	40	—
141	m—ms	40	1.7	2700	4						
241	m	23	1.5	750	70						
341	a	5	1.35	30	—						
441	w	6	1.1	40	—						

In conclusion, we wish to express our gratitude to Professor J. M. Robertson, F.R.S., for his interest in this work.

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[Received, January 13th, 1947.]

277. *The Separation of d-Fructose from Other Natural Sugars as its 2:3-4:5-Diacetone and 1:2-Monoacetone Derivatives: Observations on the Behaviour of Acetone Derivatives of Monosaccharides towards Cold Decinormal Sulphuric Acid.*

By D. J. BELL.

A simple procedure is described for the isolation of *d*-fructose from mixtures of monosaccharides as the 2:3-4:5-diacetone derivative. Glucose, mannose, xylose, and rhamnose do not interfere. The method is not applicable where galactose, arabinose, or fucose are present in quantity; in such instances a procedure leading to the isolation of 1:2-monoacetone fructose is adopted.

The diacetone derivatives of glucose, mannose, and xylose and the monoacetone derivatives of rhamnose and ribose (all understood to be derived from the furanose form of the sugars) are hydrolysed to the corresponding monoacetone compounds, or to the free sugar, by several hours' treatment with 0.1N-sulphuric acid at room temperature. On the other hand, 2:3-4:5-diacetone fructose, and the diacetone derivatives of galactose, fucose, and arabinose (all believed to have pyranose structures) resist this hydrolytic attack. 1:2-4:5-Diacetone fructose is anomalous: it behaves as if it had a furanose ring although it is generally considered to be derived from fructopyranose. Use being made of this difference in hydrolytic behaviour, a number of sugar separations are facilitated through their readily obtained acetone derivatives.

THE identification of *d*-fructose, especially in crude material of biological origin, has always presented difficulty. The only crystalline derivative hitherto employed to this end is the phenylmethylosazone (Neuberg, *Ber.*, 1902, 35, 960; Neuberg and Mandl, *Arch. Biochem.*, 1946, 11, 451). This substance is formed in variable yield; when it is isolated from mixtures its physical properties tend to be erratic, and in theory, if not in practice, it may also be formed from *d*-glucose and *d*-mannose. It is also necessary to work in relatively concentrated solutions, so the presence of large amounts of mineral matter, etc., besides other sugars, as often occur in biological extracts, complicates, or may even render impossible, isolation of the phenylmethylosazone. Work in this laboratory demanded an unequivocal means of identifying relatively small amounts (*e.g.*, 100 mg.) of *d*-fructose under conditions such as those described.

It was considered that treatment of the dried material with acetone and a suitable catalyst would provide a convenient means of separating carbohydrates (as monosaccharides) from inert material and at the same time produce derivatives which, directly or indirectly, would

lead to characterisation of the sugars, and this has proved to be the case. Irvine and Garrett (J., 1910, 97, 1283) observed that 2 : 3-4 : 5-diacetone fructose (the so-called " β "-derivative) displayed remarkable stability towards cold dilute acid, in marked contrast to the behaviour of the 1 : 2-4 : 5-isomer (" α " diacetone fructose). Ohle and Koller (Ber., 1924, 57, 1566) confirmed this finding and further noted that 1 : 2-5 : 6-diacetone glucose was, like α -diacetone fructose, unstable to cold 0.1N-sulphuric acid, both substances losing at least one isopropylidene radical by hydrolysis. Ohle and Koller further demonstrated that, although low concentration of mineral acid catalyst favoured the formation of α -diacetone fructose (cf. E. Fischer, Ber., 1895, 28, 1164; Irvine and Garrett, *loc. cit.*; Montgomery, J. Amer. Chem. Soc., 1934, 56, 419), yet increase in concentration of the catalyst led to increasing formation of the β -isomer, resulting in a series of mixed products, until, at a concentration of 4% of sulphuric acid, pure β -diacetone fructose was formed. The use of catalysts such as zinc chloride (H. O. L. Fischer and Taube, Ber., 1927, 60, 485) favours formation of the α -derivative.

In the present work the above observations have been confirmed and extended. The presence of 5% (v/v) of sulphuric acid in the acetone condensation (optimum duration, 6 hours) produces over 70% of the theoretical yield of β -diacetone fructose while diacetone glucose, under similar conditions, is formed to the extent of 50–55%. If a mixture of glucose and fructose, or sucrose itself, is treated in the above manner, the products are mainly β -diacetone fructose and diacetone glucose along with minor quantities of monoacetone derivatives. Partition of this mixture between chloroform and water leaves the "mono"-constituents in the aqueous phase. Six hours' treatment of the material obtained from the chloroform phase with 0.1N-sulphuric acid effects hydrolysis of the diacetone glucose and the α -diacetone fructose to the monoacetone derivatives; pure β -diacetone fructose is obtained by partition into chloroform. If all the "mono"-residues are brought into the dry state, recondensed with acetone, treated with dilute acid, and partitioned as before, the total yield of β -diacetone fructose may approach 80% of the theoretical.

It having been established that fructose could satisfactorily be separated from glucose, it seemed desirable to determine whether differences in hydrolytic behaviour existed among the acetone derivatives of other natural monosaccharides, and to what extent their presence might interfere with the isolation of β -diacetone fructose. The required derivatives were prepared under the conditions described above (which are not necessarily optimum for sugars other than fructose). Those compounds which are considered to be derived from the pyranose form of the parent sugar, *viz.*, the diacetone derivatives of *D*-galactose, *L*-arabinose, and *L*-fucose, all proved completely resistant to the action, for 6 hours, of 0.1N-sulphuric acid. In contrast, the furanose compounds, diacetone *D*-mannose, diacetone *D*-xylose, and monoacetone *L*-rhamnose, behaved similarly to diacetone glucose and were converted into substances which could not be extracted from water by chloroform. Crude "monoacetone *D*-ribose" (see Experimental) is hydrolysed comparatively slowly, but, although it is partitioned into chloroform, the restricted occurrence of the parent sugar is unlikely to cause difficulties. It was found practicable to isolate β -diacetone fructose from a mixture composed of 200 mg. each of *D*-fructose and six other sugars, despite the presence of both diacetone *D*-galactose and diacetone *L*-arabinose in the final product of the chloroform–water partition.

A possible explanation of the marked difference in stability towards acid exhibited by the two types of diacetone sugar may lie in the fact that in each example possessing a furanose sugar ring the labile isopropylidene radical is united through a primary alcoholic group. However, in the instance of the labile radical of α -diacetone fructose, if we assume that the hitherto accepted pyranose structure is correct, two secondary *cis*-alcoholic groups (4 and 5) are engaged. Such configurations are stable when the sugar ring is pyranose, and labile when it is furanose. The 1 : 2-monoacetone fructose derived from α -diacetone fructose is well known to possess a pyranose structure. It may be possible that α -diacetone fructose is really a derivative of fructofuranose having its isopropylidene radicals attached through positions 1 : 2 and 4 : 6, and that hydrolysis to the monoacetone derivative is accompanied by enlargement of the ring. Our present knowledge of the chemistry of the ketoses is too scanty definitely to forbid such a transformation.

If it is desired to separate fructose from sugars which form pyranose derivatives, with acetone, condensation catalysed by 0.3% (v/v) of sulphuric acid will lead to the production of α -diacetone fructose. The action of dilute acid will hydrolyse the latter to 1 : 2-monoacetone fructose which can be partitioned from chloroform into water, leaving the pyranose diacetone compounds in the organic solvent. The yield of monoacetone fructose thus obtained is good.

EXPERIMENTAL.

Evaporation of solvents was conducted below 50°, under diminished pressure. M. p.'s. are uncorrected. Measurements of optical activity were made in a 2-dm. tube. Acetone was kept, for at least 2 weeks, over calcium chloride before use.

α-Diacetone d-Fructose.—(a) *Catalyst, zinc chloride.* The method of H. O. L. Fischer and Taube (*loc. cit.*) was followed. From 2 g. of fructose, the yield (not improved by using varying amounts of catalyst) was 3.8 g., after recrystallisation from ligroin (b. p. 60–80°); m. p., 119°, $[\alpha]_D^{18}$ (water) – 161.0°; (chloroform) – 147.3°.

(b) *Catalyst, 0.3% sulphuric acid.* 5 G. of fructose were shaken with 50 ml. of dry acetone containing 0.15 ml. of concentrated sulphuric acid; after 24 hours the sugar was completely dissolved. The reaction mixture was kept for a further 24 hours, stirred with anhydrous sodium carbonate to remove acid, filtered, and evaporated. The residue was dissolved in water, the pH adjusted to 8.5–9 by addition of dilute sodium hydroxide, and the solution distilled under reduced pressure to remove mesityl oxide. The solution was then shaken with a little charcoal, filtered, and three times extracted with its own volume of chloroform. On evaporation of the dried (Na_2SO_4) extract, 5.29 g. of crystalline material were left. Recrystallised from ligroin (b. p. 60–80°), 4.79 g. (66%) of pure *α*-diacetone fructose were obtained, having m. p. 119°, $[\alpha]_D^{18}$ (chloroform) – 147.3°.

β-Diacetone Fructose.—(a) *Catalyst, 4% sulphuric acid* (cf. Ohle and Koller, *loc. cit.*). 5 G. of fructose were shaken with 50 ml. of dry acetone containing 2 ml. of sulphuric acid. The sugar dissolved rapidly and, after being kept for 3 hours, the solution was worked up in the manner described for the *α*-isomer. The crude product (3.7 g.) was crystalline; it proved, however, to consist of mixed crystals of the *α*- and the *β*-isomer which could not be separated by fractional crystallisation; m. p. ca. 80°, $[\alpha]_D^{18}$ (water) – 62.8°. (Ohle and Koller observed similar inseparable mixtures when using lower concentrations of catalyst.) This mixture corresponds to one of 25% "*α*" with 75% "*β*"; 3.2 g. were kept for 3 hours in 0.1N-sulphuric acid solution. After neutralisation of the acid with dilute sodium hydroxide, the solution was three times extracted with its own volume of chloroform. On evaporation of the solvent, 2.4 g. (75% of the mixed crystals taken) of needles, m. p. 93–94°, remained. After recrystallisation from ligroin (b. p. 60–80°), the m. p. rose to 95–96° and $[\alpha]_D^{18}$ (water) was – 33.1° (c. 7); these constants agree with those previously recorded.

(b) *Catalyst, 5% sulphuric acid.* 2.5 G. of fructose were shaken for 4 hours with 25 ml. of acetone containing 1.25 ml. of sulphuric acid, and the mixture treated as before. The chloroform phase yielded 2.7 g. (74%) of crystals, m. p. 90°, $[\alpha]_D^{18}$ (water) – 41.9°, corresponding to a mixture of 93% "*α*" with 7% "*β*".

The aqueous phase from the chloroform extraction was evaporated to dryness, and 0.5 g. of a colourless solid obtained; this was treated with 10 ml. of acetone (5% H_2SO_4) in the manner described above for 4 hours. After the customary separation by partition, 0.4 g. of crystalline diacetone fructoses was obtained, bringing the total yield to 3.1 g. 2.5 G. of this material were subjected to the action of 0.1N-sulphuric acid for 2 hours; the yield of pure *β*-diacetone fructose (m. p. 95–96°) was 2.3 g. (ca. 79%).

Ohle and Koller stated that the specific rotation (in water) of *β*-diacetone fructose varies with the concentration of the solute. That this is not the case is shown by the following observations:

Concn., g./100 ml.	7.0	3.5	1.0
$[\alpha]_D^{18}$	– 33.1°	– 33.1°	– 32.95°

The specific rotation in chloroform was also found to be – 24.8° over a range of concentrations.

The Stability of β-Diacetone Fructose towards 0.1N-Sulphuric Acid.—352 Mg. of pure *β*-diacetone fructose were dissolved in the acid, and the solution kept at room temperature for 6 hours. After the pH of the solution had been brought to about 9 by addition of sodium hydroxide, it was three times extracted with chloroform. Evaporation of the chloroform phase yielded 350 mg. (99.5%) of crystals, m. p. 95°, $[\alpha]_D^{18}$ (water) – 32.9° (c. 2.5).

Conversion of α into β-Diacetone Fructose.—1.300 G. of *α*-diacetone fructose were dissolved in 20 ml. of acetone containing 1 ml. of sulphuric acid. After being kept for 6 hours at room temperature, the product was isolated by the usual procedure. The yield of crystals was 1.202 g. (92.5%); $[\alpha]_D^{18}$ was – 32.7° (chloroform), corresponding to a mixture of 90% "*β*" with 10% "*α*". The material was therefore treated with 0.1N-sulphuric acid for 6 hours, and the *β*-diacetone fructose isolated by partition into chloroform. 1.010 G. of needles were obtained, corresponding to 93.5% of the *β*-diacetone compound estimated to be present in the product of the acetone treatment. The material had $[\alpha]_D^{18}$ (chloroform) – 24.8° (c. 5.78), and after recrystallisation from ligroin (b. p. 60–80°) melted at 95–96°.

Action of Acetone containing 5% of Sulphuric Acid on Some Monosaccharides.—The finely powdered sugar was shaken for 6 hours (unless stated to the contrary) with 20 parts (v/w) of acetone containing 5% (v/v) of the catalyst. The reaction mixture was treated as in the preparation of *α*-diacetone fructose, and the product isolated by triple chloroform extraction from water.

(a) *d*-Glucose (5 g.). Crude yield (crystalline) 4.59 g. (63%); recrystallised from ligroin (b. p. 60–80°), 3.84 g. (53%), m. p. 110°; $[\alpha]_D^{18}$ (chloroform) – 12.3° (c. 5.6).

(b) *d*-Galactose (5 g.). After 24 hours, 0.9 g. of sugar remained undissolved; yield (syrup) 3.55 g. (60%); $[\alpha]_D^{18}$ (chloroform) – 55.0° (c. 2.14), (water) – 42.8° (c. 2.77).

(c) *d*-Mannose (2 g.). 1.802 G. of crystals, m. p. 123°, were obtained. This material was pure, the m. p. not being raised by crystallisation from ethanol; $[\alpha]_D^{18}$ (methanol-water, 2:3) showed downward mutarotation, from + 7.8° to + 3.9° (const. after 24 hours) (c. 1.29). In chloroform solution (c. 5.9) similar behaviour was observed, $[\alpha]_D$ falling from + 8.7° to a constant value (24 hours) of + 5.7°.

(d) *d*-Fructose (5 g.). The crude product was treated with cold 0.1N-sulphuric acid for 6 hours. The yield of pure material (from ligroin, b. p. 60–80°) was 5.40 g. (75.8%), m. p. 95°, $[\alpha]_D^{18}$ (chloroform) – 24.6° (c. 3.9).

(e) *l*-Fucose. 535 Mg. yielded 670 mg. (84%) of syrup which crystallised (needles), m. p. 35–37°.

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Distillation in a high vacuum failed to raise the m. p. Recrystallisation was readily effected from 50% aqueous methanol, yielding needles, m. p. 35–36°, $[\alpha]_D^{25}$ (chloroform) + 53.6° (c. 2.35).

(f) l-Arabinose (5 g.). Crude yield, crystalline, 6.59 g. (86%). Recrystallised from water, the substance, 4.80 g. (66.5%) had m. p. 41–42° and $[\alpha]_D^{25}$ (water) + 5.4° (c. 2.88), (chloroform) – 13.2° (c. 4.2).

(g) d-Xylose (2 g.). Crude yield (syrup) 1.82 g. (59.5%), $[\alpha]_D^{25}$ (water) + 13.0° (c. 1.32), (chloroform) + 5.0° (c. 2.68).

(h) d-Ribose. 270 Mg. yielded 129 mg. of a syrupy "monoacetone" condensation product.

Although a reasonable yield is in each instance obtainable by the above procedure, it is emphasised that, the preparation of β -diacetone fructose excepted, methods already described in the literature may for individual examples prove superior.

Recovery of Acetone Sugars after Treatment with Cold 0.1N-Sulphuric Acid.—Weighed amounts of the sugars were condensed with acetone (5% sulphuric acid) for 6 hours, and the products, isolated by the procedure described above, subjected to the action of 0.1N-sulphuric acid at room temperature for the times stated. Any material extractable by chloroform was then recovered and weighed. The findings are tabulated below:

Sugar.	Wt. used, mg.	Hrs. in acid:		Yield (%) of sugar taken.		Diacetone cpd. resistant to 0.1N-H ₂ SO ₄ , %.
		2.	6.	2.	6.	
d-Glucose	500	82	0	11.3	0	0
d-Mannose	500	80	0	11.0	0	0
d-Xylose	500	49	0	6.4	0	0
l-Rhamnose	500	55 *	0	8.9 *	0	0
d-Ribose.....	270	—	50 †	—	14.6 *	—
d-Galactose	390	345	340	68	65	95.6
l-Arabinose	500	663	663	86.4	86.4	100
l-Fucose	535	670	633	84.2	83.3	94.4

* Monoacetone derivatives.

† This material is probably a mixture of 2 : 3-monoacetone ribofuranose with the anhydro-derivative described by Levene and Stiller (*J. Biol. Chem.*, 1933, **102**, 187); sufficient material was not available for accurate investigation.

Monoacetone d-ribose is considered by Levene and Stiller (*loc. cit.*) to be substituted in positions 2 and 3 and to have a furanose ring; the behaviour of the crude product described above is intermediate between those compounds which have furanose rings and those resistant substances where the sugar ring is pyranose. It is possible that the acid-resistant portion is the anhydro-fraction of the crude material.

Fission of Sucrose : Separation of d-Fructose from d-Glucose.—1.00 G. of finely powdered sucrose was shaken for 6 hours with 20 ml. of dry acetone containing 1.25 ml. of sulphuric acid. The crude product, isolated by the customary procedure, was a crystalline mixture of diacetone glucose with the two diacetone fructoses. Treatment of this with 0.1N-sulphuric acid for 6 hours, followed by partition between chloroform and water, yielded 0.66 g. (86.8%) of crystalline material which, after recrystallisation from ligroin (b. p. 60–80°), weighed 0.593 g. (78%) and had m. p. 95° and $[\alpha]_D^{25}$ (chloroform) – 24.7° (c. 5.2).

Separation of β -Diacetone Fructose from a Mixture of Seven Monosaccharides.—A mixture of 200 mg. of each of the following sugars was treated in the manner described for the foregoing experiment: d-glucose, d-galactose, d-mannose, l-arabinose, d-xylose, l-rhamnose, and d-fructose. After the acid treatment the crude product became partly crystalline. As it weighed 450 mg. it obviously contained diacetone galactose and diacetone arabinose as well as β -diacetone fructose. The crystals were drained on porous tile, after trituration with ice-cold ligroin (b. p. below 40°); recrystallisation in the usual way yielded 90 mg. of β -diacetone fructose, m. p. 95° alone or mixed with authentic substance.

Separation of Fructose, as the 1 : 2-Monoacetone Derivative, from a Sugar yielding an Acid-stable Diacetone Derivative.—If the mixture of sugars is condensed with acetone containing 0.3% of sulphuric acid as catalyst, as noted above, the fructose yields the acid-unstable α -diacetone derivative. (Galactose and arabinose yield 11% and 90% of their respective diacetone derivatives.) A mixture of 1.008 g. of α -diacetone fructose with 1.046 g. of diacetone galactose was kept in 0.1N-sulphuric acid solution for 4 hours at 16°. The unchanged diacetone galactose was extracted with chloroform, as in preceding experiments. The aqueous phase was made alkaline (phenolphthalein) with potassium hydrogen carbonate and heated at 100° for 30 minutes to destroy traces of reducing sugar. The solution was then evaporated, and the solid residue extracted three times with 50 ml. portions of boiling, dry ethyl acetate. On evaporation of this extract, 0.76 g. (89%) of nearly pure, crystalline 1 : 2-monoacetone d-fructose was obtained; m. p. 119°, $[\alpha]_D^{25}$ (water) – 158.8°. After recrystallisation from dry ethyl acetate, the m. p. rose to 121–122° and $[\alpha]_D^{25}$ (water) was – 159.4° (c. 3.4). From the chloroform phase of the partition 0.981 g. of diacetone d-galactose was recovered after evaporation of the solvent.

The author is grateful to Professor A. R. Todd and Dr. E. G. V. Percival for gifts of d-ribose and l-fucose. The financial support of the Agricultural Research Council is thankfully acknowledged.

278. The Reaction between Trialkyl Phosphites and Alkyl Halides.

By A. H. FORD-MOORE and J. HOWARTH WILLIAMS.

The rearrangement of trialkyl phosphites (Arbusov) has been extended so as to afford a simple method for preparing the dialkyl esters of alkyl- and halo-alkyl-phosphonic acids. When the halogen (bromine) atom in diethyl halogeno-alkylphosphonates is in the β -position to the phosphorus, hydrogen bromide is readily lost, giving dialkyl alkylenephosphonates.

THE Arbusov rearrangement in its simplest form (*Chem. Zentr.*, 1906, II, 1640) consists of the isomerisation of a trialkyl phosphite to a dialkyl alkylphosphonate (in 95% yield) by warming it with the corresponding alkyl iodide. Arbusov and Kushkova (*J. Gen. Chem. Russia*, 1936, 6, 283) extended the reaction to methylene iodide and found that when this compound was heated with triethyl phosphite (I), diethyl iodomethylphosphonate could be isolated from the reaction mixture.

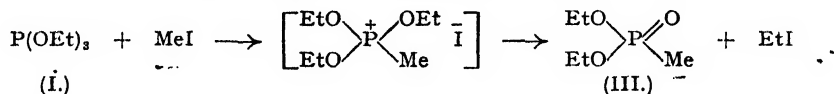
Later, Kosolapoff (*J. Amer. Chem. Soc.*, 1944, 66, 1511) reinvestigated the reaction between (I) and butyl bromide, hexyl bromide, ethylene bromide, and trimethylene bromide. He found that when the first three bromides were heated with (I), ethyl bromide was eliminated and some diethyl ethylphosphonate (II) formed. He was unable to isolate any other product of the reaction. With trimethylene bromide, he obtained some tetraethyl trimethylenediphosphonate and diethyl 3-bromopropylphosphonate, the latter as the free acid after hydrolysis.

In our hands, the Arbusov rearrangement was found to be of much wider application and can be used for preparing several series of compounds. In all cases except one (in which triisopropyl phosphite was used), the reaction was carried out with (I).

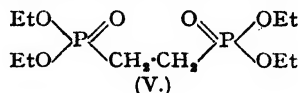
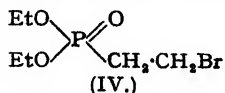
When (I) is warmed with an equimolar quantity of methyl iodide for a short time, a vigorous reaction sets in, and, on fractionation of the product, almost quantitative yields of ethyl iodide and diethyl methylphosphonate (III) are obtained. The reaction between methyl iodide and triisopropyl phosphite proceeds even more easily, the products being isopropyl iodide and diisopropyl methylphosphonate.

The interaction of (I) and ethylene bromide was next examined. If the reaction is carried out under reflux, the mixture on fractionation gives ethyl bromide, a considerable amount of (II), and a high boiling residue.

The reaction between (I) and methyl iodide gives strong support to the suggestion that the rearrangement takes place through the formation of an unstable phosphonium halide. In this particular case, the larger radical is eliminated as halide:



It seemed probable, therefore, that, in the reaction between (I) and ethylene bromide, if the ethyl bromide were allowed to escape, the amount of high-boiling residue formed would increase at the expense of the (II). This was found to be so. When the reaction was carried out under a column so that the ethyl bromide distilled out as fast as it was formed, the residue of high-boiling material was considerably greater. This, on further distillation at 1–2 mm., was found to be a mixture of diethyl 2-bromoethylphosphonate (IV) and tetraethyl ethylene-



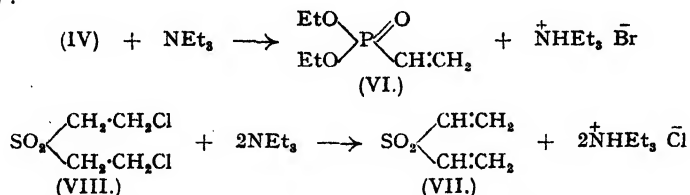
1 : 2-diphosphonate (V). Contrary to the observation of Kosolapoff (*loc. cit.*), they both appear to distil at this pressure without decomposition.

This reaction can be extended to primary alkyl bromides. With *n*-hexyl bromide or higher homologues, the reaction proceeds very smoothly giving ethyl bromide and a small amount of (II), most of the product consisting of the diethyl alkylphosphonate, isolated by distillation in a vacuum. The reaction of (I) with *n*-amyl bromide goes less easily; with *n*-butyl bromide and isoamyl bromide, it takes place very sluggishly; ethyl bromide is slowly evolved, a considerable amount of (II) is formed, and the yield of alkylphosphonate is poor. No reaction between secondary bromides, such as cyclohexyl bromide and 2-bromo-octane, and (I) takes place.

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When methylene bromide is used, the reaction goes slowly and a poor yield of tetraethyl methylenediphosphonate results, the bromomethylphosphonic ester being almost entirely absent. No difficulty is experienced in obtaining the methylenediphosphonate when methylene iodide is used in place of the bromide, the iodomethylphosphonic ester being formed simultaneously (cf. Arbusov and Kushkova, *loc. cit.*). With trimethylene bromide, we had no difficulty in obtaining tetraethyl trimethylenediphosphonate, but we were unable to prepare the bromopropylphosphonate either pure or in any quantity.

(IV) undergoes an interesting reaction on treatment with triethylamine in dry benzene. Triethylamine hydrobromide is formed, and diethyl vinylphosphonate (VI) can be isolated from the residue by distillation under reduced pressure. This reaction recalls the preparation of divinyl sulphone (VII) from 2 : 2'-dichlorodiethyl sulphone (VIII) (Alexander and McCombie, *J.*, 1931, 1913) :



Unlike (VII), which reacts with thiophenol with evolution of heat [to give 2 : 2'-bis(phenylthioethyl) sulphone], no reaction takes place between thiophenol and (VI).

Since secondary bromides do not enter into this reaction, we hoped to prepare diethyl 2-bromopropylphosphonate (IX) by the interaction of propylene bromide and (I); (IX) should lose HBr on treatment with triethylamine to give diethyl propenylphosphonate (X) :



When (I) and propylene bromide are heated, ethyl bromide distils but no trace of (IX) can be isolated, the product consisting of (II) together with a rather poor yield of (X).

The (I) used in these reactions was prepared by the method of McCombie, Saunders, and Stacey (*J.*, 1945, 380) who obtained it by the action of phosphorus trichloride on ethanol in ether in the presence of dimethylaniline. We found that the dimethylaniline could be replaced with advantage by diethylaniline and the ether by light petroleum (b. p. 40–60°). The diethylaniline hydrochloride formed is non-hygroscopic, a 95% recovery of the base is obtained without difficulty, and the yield of (I) is at least 85%.

EXPERIMENTAL.

Triethyl Phosphite (I).—This, prepared in 87–92% yield by the method of McCombie, Saunders, and Stacey (*loc. cit.*) but with light petroleum (b. p. 40–60°) and diethylaniline in place of ether and dimethylaniline, had the following constants: b. p. 52°/14 mm., 57°5'/19 mm. (McCombie, Saunders, and Stacey give b. p. 48°/12.5 mm.), d_{15}^{20} 0.963, n_D^{20} 1.4140.

Triisopropyl phosphite was prepared similarly, but owing to the closeness of its b. p. to that of diethylaniline, an equivalent amount of pyridine, or, better, triethylamine was used in place of the former.

Diethyl Methylphosphonate (III).—(I) (55 g.) and methyl iodide (50 g.) were refluxed gently for 2 hours on a steam-bath. On distillation at ordinary pressure, ethyl iodide (50 g.) was recovered. The residue distilled in a vacuum gave **diethyl methylphosphonate** (52.5 g.; 95%), b. p. 64–65°/2 mm., n_D^{20} 1.4120 (Found: C, 39.18; H, 8.83. $\text{C}_6\text{H}_{13}\text{O}_3\text{P}$ requires C, 39.47; H, 8.55%).

Diisopropyl methylphosphonate was obtained similarly from triisopropyl phosphite and methyl iodide in 95% yield. The reaction is vigorous and the conversion complete within a few minutes; b. p. 66°/3 mm., n_D^{20} 1.4120 (Found: C, 45.95; H, 9.53. $\text{C}_7\text{H}_{15}\text{O}_3\text{P}$ requires C, 46.66; H, 9.44%).

The Diethyl Alkylphosphonates.—Diethyl ethylphosphonate (II) was prepared in 95% yield by the method of Arbusov (*loc. cit.*) from (I) and ethyl iodide; b. p. 62°/2 mm., d_{15}^{20} 1.032, n_D^{15} 1.4172.

Diethyl n-dodecylphosphonate. (I) (62.5 g.) and n-dodecyl bromide (94 g.) were heated under a column attached to a condenser set for distillation. At about 160°, ethyl bromide started to distil. After about 1.5 hours, ethyl bromide (31.5 g.) stopped distilling and the mixture was fractionated under reduced pressure to give: (II) (7 g.), b. p. 60–70°/3 mm.; dodecyl bromide (8 g.), b. p. 124°/1 mm.; **diethyl n-dodecylphosphonate** (73 g.), b. p. 160°/1 mm., n_D^{20} 1.4419 (Found: C, 62.86; H, 11.60. $\text{C}_{14}\text{H}_{31}\text{O}_3\text{P}$ requires C, 62.74; H, 11.51%).

The following esters were obtained similarly. **Diethyl n-butylphosphonate**, b. p. 74°/1 mm., n_D^{17} 1.4244 (Found: C, 47.40; H, 10.21. $\text{C}_8\text{H}_{19}\text{O}_3\text{P}$ requires C, 49.49; H, 9.86%). **Diethyl n-amylphosphonate**, b. p. 86°/1.5 mm., $n_D^{16.5}$ 1.4282 (Found: C, 51.12; H, 10.36. $\text{C}_9\text{H}_{21}\text{O}_3\text{P}$ requires C, 51.90; H, 10.17%). **Diethyl n-hexylphosphonate**, b. p. 103°/2 mm., n_D^{17} 1.4311 (Found: C, 53.34; H, 10.58. $\text{C}_{10}\text{H}_{23}\text{O}_3\text{P}$ requires C, 54.08; H, 10.43%). **Diethyl n-heptylphosphonate**, b. p. 113°/1.9 mm., $n_D^{16.5}$

1.4325 (Found: C, 54.90; H, 10.87. $C_{11}H_{18}O_3P$ requires C, 55.90; H, 10.66%). *Diethyl n-octylphosphonate*, b. p. $119^\circ/1.2$ mm., n_D^{20} 1.4360 (Found: C, 57.54; H, 10.88. $C_{13}H_{27}O_3P$ requires C, 57.59; H, 10.88%). *Diethyl 3-methyl-n-butyl-1-phosphonate*, b. p. $75^\circ/0.8$ mm., n_D^{20} 1.4266 (Found: C, 51.54; H, 10.26. $C_8H_{17}O_3P$ requires C, 51.90; H, 10.17%).

Diethyl 2-bromoethylphosphonate (IV). (I) (83 g. = 0.5 mol.) and ethylene bromide (141 g. = 0.75 mol.) were heated as in the preparation of the dodecylphosphonic ester described above. The reaction was complete in about two hours, 48 g. of ethyl bromide having distilled. The residue on fractionation under reduced pressure gave the following products: recovered ethylene bromide, 77 g.; (II) b. p. $60-70^\circ/3$ mm., 15 g.; *diethyl bromoethylphosphonate*, b. p. $101^\circ/0.8$ mm., n_D^{20} 1.4600, 48.5 g. (Found: C, 29.71; H, 5.96. $C_8H_{14}O_3BrP$ requires C, 29.40; H, 5.76%); tetraethyl ethylenediphosphonate, (g.v.), b. p. $167^\circ/1$ mm.

Diethyl iodomethylphosphonate, b. p. $101^\circ/0.7$ mm., n_D^{20} 1.4975 (Found: C, 21.94; H, 4.58. Calc. for $C_8H_{13}O_3IP$: C, 21.60; H, 4.36%) and *tetraethyl methylenediphosphonate*, b. p. $143^\circ/1.5$ mm., n_D^{20} 1.4312 (Found: C, 35.68; H, 7.67. $C_8H_{12}O_6P_2$ requires C, 37.51; H, 7.70%) were obtained similarly by substituting methylene iodide for ethylene bromide. Tetraethyl methylenediphosphonate was also obtained by using methylene bromide in place of methylene iodide, but in poor yield; the expected diethyl bromomethylphosphonate was almost entirely absent.

Diethyl vinylphosphonate (VI). (IV) (48.5 g.), triethylamine (22 g. = 30 c.c.), and benzene (70 c.c.) were refluxed for 1 hour. After standing overnight, the triethylamine hydrobromide was filtered off, the benzene distilled from the filtrate, and the residue fractionated under reduced pressure. *Diethyl vinylphosphonate* (26 g.), n_D^{20} 1.4320, distilled at $63^\circ/2.5$ mm. (Found: C, 43.54; H, 8.37. $C_8H_{13}O_3P$ requires C, 43.88; H, 7.98%).

Tetraethyl ethylenediphosphonate (V). (I) (157 g.) and ethylene bromide (100 g. = 47 c.c.) were allowed to react as in the preparation of (IV) and the product was worked up similarly. Ethyl bromide (75 g.) distilled during the reaction, and the residue gave the following fractions: (II), b. p. $55-60^\circ/2$ mm., 55 g.; (IV), b. p. $99-115^\circ/1$ mm., 18 g.; *tetraethyl ethylenediphosphonate*, b. p. $167^\circ/1$ mm. ($180^\circ/2.5$ mm.), 71 g., n_D^{20} 1.4425 (Found: C, 39.26; H, 7.96. $C_{10}H_{24}O_6P_2$ requires C, 39.73; H, 8.00%).

Tetraethyl trimethylenediphosphonate. This was made similarly from (I) and trimethylene bromide; it had b. p. $175^\circ/0.8$ mm., n_D^{20} 1.4508 (Found: C, 40.34; H, 8.18. Calc. for $C_{11}H_{26}O_6P_2$: C, 39.73, H, 8.29%).

When (I) and 1:2-dibromopropane were similarly treated, no diethyl 2-bromopropylphosphonate could be isolated. After repeated fractionation under reduced pressure, the product was *diethyl propenylphosphonate* (X), b. p. $78-81^\circ/2$ mm., n_D^{20} 1.4320 (Found: C, 46.60; H, 8.79. $C_7H_{14}O_3P$ requires C, 47.19; H, 8.49%).

The microanalyses were carried out by Mr. W. Brown. The consistently low values found for carbon are probably due to the difficulty in effecting the complete combustion of these substances.

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[Received, January 15th, 1947.]

279. Lanosterol. Part IV. Hydrocarbons formed by the Action of Dehydrating Agents.

By CHARLES DORÉE, JAMES F. MCGHIE, and FREDERICK KURZER.

Phosphorus oxychloride and pentachloride have proved effective dehydrating agents in the lanosterol group. Thus, dihydrolanosterol, according to the reagent and conditions employed, yields two isomeric hydrocarbons of the formula $C_{30}H_{50}$, α -lanostadiene, and isolanostadiene, respectively. Dihydroagnosterol (γ -lanosterol) and other members of this series are dehydrated with equal facility to the corresponding hydrocarbons. A new alternative method for the preparation of α -lanostene (Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, 27, 479) is also described, and the relationship between these hydrocarbons is discussed in connection with the position of the unsaturated centres in the molecule.

THE experimental facts established in previous researches in regard to lanosterol are the formula, $C_{30}H_{50}O$, and the presence of one secondary hydroxyl group and two double bonds—one reactive and one inert—in a tetracyclic, triterpenoid nucleus, with a side-chain of at least four carbon atoms terminating in an isopropylidene group, in which the reactive double bond is incorporated. It was known that the lanosterol fraction obtained from wool-grease contained approximately 10% of the analogous triply unsaturated alcohol agnosterol, $C_{30}H_{48}O$. More recently, Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, 27, 479; *ibid.*, 1945, 28, 759) have recognized the presence of both dihydrolanosterol and dihydroagnosterol, and lanosterol has been shown to be identical with the cryptosterol of yeast. The agnosterol compounds can be removed by exhaustive crystallization, leaving a non-separable mixture of lanosterol and its dihydro-derivative, which hitherto has been described as lanosterol. Lanosterol (cryptosterol) has been obtained from this by oxidation, followed by separation and reduction of the ketones. The non-separable mixture, on hydrogenation, yields pure dihydrolanosterol which is suitable for experimental work.

An examination of the hydrocarbons derived from lanosterol and its analogues was undertaken to obtain evidence of the relationship between lanosterol and other tetracyclic triterpenes, and to make available new compounds for structural investigation. The fully saturated parent hydrocarbon lanostane has not yet been obtained. Lanostene, corresponding to lanosterol, and hydrocarbons derived from dihydrolanosterol, dihydroagnosterol (γ -lanosterol), and isodihydrolanosterol have been prepared by Ruzicka *et al.* (*loc. cit.*). The procedure employed in each case was to prepare the ketone, the semicarbazone of which was reduced, according to the Wolff-Kishner method, with sodium and ethanol under pressure. A simple and convenient modification has now been found in the direct reduction of ketone to hydrocarbon, using a modified form of the Clemmensen reaction with amalgamated zinc and hydrochloric acid. Under the conditions of experiment the hydrochloric acid does not cause bond-movement, and good yields of the desired hydrocarbons are readily obtained.

A systematic examination of the action of dehydrating agents on dihydrolanosterol has resulted in a new approach to hydrocarbons containing an additional double bond. In the dehydrations studied, the unsaturated linkage would be introduced by the removal of the hydroxyl group and the hydrogen of an adjacent carbon atom of the ring system. Provided that bond-movement does not take place, therefore, the location of the newly formed double bond is limited with great probability to a single position in the ring containing the hydroxyl group.

Most of the dehydrating agents that have been successfully employed in the case of the sterols and triterpenes were found unsuitable for dehydration in the lanosterol series. Anhydrous copper sulphate in xylene, activated alumina at temperatures up to 250°, *p*-toluenesulphonyl chloride in boiling pyridine, and acetic anhydride-sulphuric acid mixtures failed to yield products of dehydration. On the other hand, the halides and oxyhalides of phosphorus, particularly the oxychloride and pentachloride, proved highly satisfactory, giving hydrocarbons smoothly and in excellent yield.

Phosphorus oxychloride, applied by Heilbron (*J.*, 1935, 1223) in the conversion of lumisterol into lumistatetraene, when acting on dihydrolanosterol under analogous conditions gave a non-homogeneous reaction product from which α -lanostadiene was isolated. γ -Lanosterol (dihydroagnosterol) similarly gave a trebly unsaturated hydrocarbon, γ -lanostatriene. α -Lanostadiene showed no characteristic absorption in the ultra-violet, but γ -lanostatriene gave absorption maxima almost identical with those of γ -lanosteryl acetate (Bellamy and Dorée, *J.*, 1941, 178), indicating that the system of conjugated double bonds is still present. The newly formed unsaturated linkage is remote from this system, as the characteristic absorption curve is not altered, though the intensities are higher in the case of the hydrocarbon, as shown by the following measurements:

	$\lambda_{\max.}$	$E_{1\text{ cm.}}^{1\%}$	$\lambda_{\max.}$	$E_{1\text{ cm.}}^{1\%}$	$\lambda_{\max.}$	$E_{1\text{ cm.}}^{1\%}$
γ -Lanosteryl acetate	238	300	245	380	250	250
γ -Lanostatriene	237	400	243	440	254	320

Lanostadiene has an increased reactivity due to the additional double bond which, unlike the inert double bond in dihydrolanosterol, shows a reactivity approaching that of an ethylenic linkage. Its probable location in the terminal ring of the triterpene molecule, already suggested by its mode of formation, is supported by the properties of the hydrocarbon. Thus, α -lanostadiene readily adds two atoms of hydrogen in the presence of contact catalysts forming α -lanostene, which is identical with Ruzicka's "dihydrolanostene", obtained by Wolff-Kishner reduction of dihydrolanostenone semicarbazone. Similarly, α -lanostene rapidly absorbs two atoms of bromine: the addition product is highly labile, however, and decomposes at once forming a halogen-free compound, provisionally designated isomer X. Lanostadiene is readily isomerized by hydrogen chloride yielding β -lanostadiene, and it can be dehydrogenated to yield products of still higher unsaturation. The action of either selenium dioxide in anhydrous ethanol or *N*-bromosuccinimide afford excellent yields of α -lanostatriene. This triene shows no absorption in the ultra-violet, indicating the absence of a system of conjugated double bonds, and its non-identity with γ -lanostatriene.

Opening of the terminal ring of α -lanostadiene by controlled oxidative fission under various conditions has been attempted, but no crystallisable substances have so far been isolated from the large yields of acidic reaction products obtained.

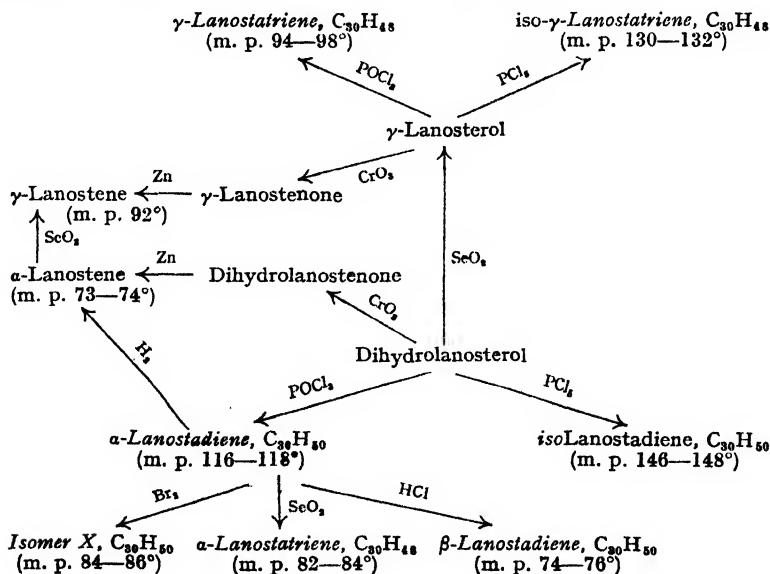
Phosphorus pentachloride has also proved a useful dehydrating reagent. α -Amyranonol, for example, in light petroleum solution is converted into α -amyradienone (Spring and Vickerstaff, *J.*, 1937, 251), while 3(β)-acetoxysterol-7- β -ol can be similarly dehydrated using the reagent in the presence of calcium carbonate in anhydrous media (Wintersteiner and

Moore, J. *Amer. Chem. Soc.*, 1943, **65**, 1507). Phosphorus pentachloride, acting on dihydrolanosterol in boiling light petroleum solution, gave excellent yields of a doubly unsaturated hydrocarbon, *isolanostadiene*. Wieland, when dehydrating dihydrocryptosterol by high vacuum distillation with boron trioxide at 350° (Wieland and Joost, *Annalen*, 1941, **546**, 119) obtained a cryptostadiene, $C_{30}H_{50}$. Since the identity of lanosterol and cryptosterol has been established by Ruzicka *et al.* (*Helv. Chim. Acta*, 1945, **28**, 759) and by ourselves, there seems little doubt that *isolanostadiene* is identical with Wieland's cryptostadiene.

isoLanostadiene and α -lanostadiene, prepared from dihydrolanosterol by the action of phosphorus pentachloride and oxychloride respectively, are isomeric. Unlike α -lanostadiene, *isolanostadiene* does not undergo hydrogenation, does not readily absorb bromine, and is considerably more resistant to chromic acid oxidation. The double bond in *isolanostadiene* is therefore far less reactive than that in α -lanostadiene, and its absence from the six-membered terminal ring (presumably owing to bond movement) can be assumed. This view is supported by spectrometric evidence. While α -lanostadiene is transparent over the spectral range in the ultra-violet, *isolanostadiene* shows a distinct absorption maximum at 235 m μ , suggesting the presence of a system of conjugated double bonds and consequently the close proximity of the centres of unsaturation. If the isomerism of the two products, however, was entirely due to the migration of the reactive double bond of α -lanostadiene under the influence of hydrochloric acid, α -lanostadiene should be readily convertible into the *iso*-compound by treatment with anhydrous hydrogen chloride. As already mentioned, however, α -lanostadiene when treated with either hydrogen chloride or phosphorus pentachloride does not yield *isolanostadiene*, but an entirely new isomer, β -lanostadiene. The observed facts can therefore not be accounted for by a consideration of geometrical isomerism alone. A retropinacoline rearrangement of the type recently described by Ruzicka *et al.* (*Helv. Chim. Acta*, 1945, **28**, 767, 942, 1628; 1946, **29**, 210), occurring when α -amyranonol, lupeanol, and oleanolic acid lactone are treated with phosphorus pentachloride, may possibly take place in the analogous formation of *isolanostadiene*. Experiments to obtain further information on the nature of these isomers are in progress.

Phosphorus pentachloride has proved equally satisfactory in the dehydration of related compounds. When applied to γ -lanosterol (dihydroagnosterol), for example, the procedure furnishes good yields of *iso*- γ -lanostatriene.

The relationships of these hydrocarbons are shown in the scheme below :



EXPERIMENTAL.

Melting points are uncorrected. The rotation measurements, for which the authors are indebted to Mr. H. Heath, were made in chloroform solution at 15°.

α -Lanostene ("Dihydrolanostenone").—A hot solution of dihydrolanostenone (5 g.; 1 mol.) in glacial acetic acid (150 ml.) was added to amalgamated zinc filings (40 g.; 50 mols.) and the mixture boiled. On

addition of concentrated hydrochloric acid (40 ml.; 30 mols.) vigorous reaction took place, and refluxing was continued for 1½ hours. The clear acetic acid solution was poured into water (600 ml.) and the crude dihydrolanostene, separating as a white flocculent precipitate, isolated by extraction with ether. The extracts were washed with sodium hydroxide solution and with water until neutral, and the colourless oily residue obtained on removal of the solvent further purified by filtration of its petroleum solution through alumina. After 3 recrystallisations from chloroform-methyl alcohol (1:5), α -lanostene (2–2.5 g.), m. p. 73–74°, $[\alpha]_D + 66.2^\circ$ (c, 0.90), was obtained in lustrous plates (Found: C, 87.58; H, 12.40. Calc. for $C_{30}H_{52}$: C, 87.38; H, 12.62%).

γ -Lanostene.—(a) γ -Lanostenone, when treated with amalgamated zinc as described above, gave 40–50% yields of γ -lanostene, forming shining plates, m. p. 89–91°, $[\alpha]_D + 77^\circ$ (c, 1.04) (Found: C, 87.99; H, 12.05. Calc. for $C_{30}H_{50}$: C, 87.81; H, 12.19%).

(b) A solution of dihydrolanostene (3 g.; 1 mol.) was refluxed with excess of selenium dioxide (3 g.; 4 mols.) in glacial acetic acid (50 ml.) for 2 hours. The separated selenium was removed, and the filtrate deposited crystalline γ -lanostene on cooling and standing. After two recrystallisations from chloroform-ethyl acetate-methyl alcohol (1:1:4), pure γ -lanostene, m. p. 90–92°, was obtained.

α -Lanostadiene.—To a solution of dihydrolanosterol (10 g.; 1 mol.) in pyridine (100 ml.) excess of phosphorus oxychloride (15 ml.; 7 mols.) was added slowly with shaking. The temperature of the mixture rose sharply to 80°. After being heated on the steam-bath for 1½ hours, the whole was boiled gently for 3 minutes and allowed to cool to room temperature. The dark brown liquid was then slowly treated with water under cooling; the crude reaction product then appeared in suspension. After repeated extraction with ether, the combined extracts were shaken with concentrated hydrochloric acid to remove pyridine, followed by repeated washings with distilled water until nearly neutral. The yellow mobile oil obtained, on removal of the solvent, was taken up in light petroleum (500 ml.) and filtered through a 25 g. alumina column. A clear colourless eluate was obtained. The yellow oil remaining after distillation of the solvent was crystallised from chloroform-acetone-methyl alcohol (30, 30, and 100 ml. respectively) to give good yields (ca. 7 g.) of a white microcrystalline mass. The material melted between 95° and 112° (signs of sintering at 85°). After repeated crystallisation from chloroform-methyl alcohol, α -lanostadiene, m. p. 114–117°, was obtained in minute white needles (2.5–3 g.). From the mother liquors there resulted a further crop (3–4 g.) of inferior material. The final fractions separated as an uncrystallisable oil (1–2 g.).

α -Lanostadiene forms microcrystalline white needles, m. p. 116–118°, $[\alpha]_D + 113^\circ$ (c, 1.040), slightly Beilstein-positive, giving a brown colour with tetranitromethane. It is soluble in chloroform, ethyl acetate, and acetone, sparingly soluble in methyl alcohol and hot glacial acetic acid (Found: C, 87.73; H, 12.26. $C_{30}H_{50}$ requires C, 87.81; H, 12.19%). Lanostadiene is optically transparent in the ultra-violet. It yields no addition product in the Diels-Alder reaction, and the absence of a system of conjugated double bonds may be inferred. It is readily reduced to α -lanostene.

A solution of α -lanostadiene (2.5 g., 1 mol.) in glacial acetic acid (150 ml.) was treated with hydrogen at 100° at ordinary pressure in the presence of finely divided platinum. Absorption of hydrogen took place rapidly, a total of 115 ml. being taken up within 10 minutes (theory, 130 ml.). Shaking was continued for another 30 minutes. After removal of the platinum the filtrate was distilled in a vacuum to small bulk (20 ml.) and the crude reaction product isolated from the residue, previously diluted with water (100 ml.), by extraction with ether. The ethereal extracts were washed with sodium hydroxide solution and with water and the solvent was removed. The residual oil, after filtration of its light petroleum solution through alumina, was crystallised thrice from chloroform-ethyl acetate-methyl alcohol, when α -lanostene was obtained in minute white plates, m. p. 70–74°, $[\alpha]_D + 65.7^\circ$ (c, 0.556), showing no depression of the melting point in admixture with α -lanostene obtained by the reduction of dihydrolanostenone (Found: C, 87.62; H, 12.40%).

Isomer X.— α -Lanostadiene (3 g.; 1 mol.), dissolved in anhydrous ether (60 ml.) was treated at 0°, within 5 minutes, with the theoretical amount of bromine dissolved in anhydrous ether (3.7 ml. of 10% v/v solution; 2 g.-atoms). The bromine solution was decolourised instantaneously; after 10 minutes' standing at 0° the ether was removed under reduced pressure, the slightly fuming yellow oil taken up in light petroleum (b. p. 60–80°; 200 ml.) and purified chromatographically. After three crystallisations from ethyl acetate-acetone-methyl alcohol, a halogen-free product, isomer X, m. p. 84–86°, $[\alpha]_D + 124^\circ$ (c, 0.372), was obtained in colourless lustrous elongated plates; ultra-violet absorption spectrum showed no absorption between 230 and 500 $m\mu$ (Found: C, 87.78; H, 12.21. $C_{30}H_{50}$ requires C, 87.81; H, 12.19%).

α -Lanostatriene.—(a) α -Lanostadiene (4 g.; 1 mol.) dissolved in ethanol (350 ml.) was treated with excess of selenium dioxide (3 g.; 3 mols.) and refluxed gently for 8 hours. The solvent was removed in a vacuum, the dark brown residue taken up in ether, and freed from traces of selenium by extraction with sodium cyanide solution. The crude reaction product in light petroleum solution was filtered through a comparatively large alumina column (30 g.). The intense yellow colour of the eluate, however, was retained after two such purifications. On crystallisation of the residue from chloroform-acetone-methyl alcohol, α -lanostatriene, m. p. 82–84°, $[\alpha]_D + 138^\circ$ (c, 0.796), was obtained in pale yellow needles; no characteristic absorption between 230 and 500 $m\mu$ (Found: C, 88.12; H, 11.83. $C_{30}H_{48}$ requires C, 88.23; H, 11.76%).

(b) α -Lanostadiene (2.5 g.; 1 mol.), dissolved in anhydrous carbon tetrachloride (60 ml.), was refluxed with excess of *N*-bromosuccinimide (1.5 g.; 1.6 mols.) for 1½ hours. Hydrogen bromide was given off throughout the reaction. After cooling, the succinimide was removed, the filtrate washed until neutral and concentrated. The oily residue was purified through an alumina column, and, after three recrystallisations from chloroform-acetone-methyl alcohol, gave α -lanostatriene in lustrous needles, m. p. 82–84°, $[\alpha]_D + 138^\circ$ (c, 0.362), identical with the product obtained by selenium dioxide dehydrogenation.

β -Lanostadiene.— α -Lanostadiene (2.5 g.), dissolved in anhydrous chloroform (50 ml.), was boiled under reflux, and hydrogen chloride passed through the solution for 3 hours. The clear green liquid obtained was washed until neutral and concentrated under reduced pressure. The residual oil, after

purification through alumina of its light petroleum solution, was crystallised thrice from chloroform-acetone-methyl alcohol, when β -lanostadiene was obtained in white needles, m. p. 74–76°, $[\alpha]_D + 128^\circ$ (c, 0.806); no characteristic absorption between 230 and 500 $m\mu$ (Found: C, 87.75; H, 12.28. $C_{30}H_{50}$ requires C, 87.81; H, 12.19%).

γ -Lanostatriene.— γ -Lanosterol (3 g.; 1 mol.), dissolved in pyridine (30 ml.) was treated with excess of phosphorus oxychloride (6 ml.; 10 mols.) at 100° for 1½ hours. On isolation of the product as described under α -lanostadiene, colourless lustrous plates of γ -lanostatriene were obtained in 60% yield, m. p. 94–98°, $[\alpha]_D + 133^\circ$ (c, 0.568) (Found: C, 88.06; H, 11.93. $C_{30}H_{48}$ requires C, 88.23; H, 11.76%). Ultra-violet absorption spectrum: Maxima at 237, 243, 254 $m\mu$; ($E_{1\%}^{1cm} = 400, 440, \text{ and } 320$ respectively), giving an absorption curve practically identical with that of γ -lanosteryl acetate (J., 1941, 178).

isoLanostadiene.—Dihydrolanosterol (10 g.; 1 mol.) dissolved in light petroleum (150 ml., b. p. 60–80°), was treated with excess of phosphorus pentachloride (10 g.; 2 mols.). Reaction took place with warming, and, after 2 hours at room temperature, dehydration was completed by refluxing for 1 hour on the steam-bath. The phosphorus pentachloride dissolved rapidly, hydrogen chloride being evolved throughout the reaction. The clear liquid was allowed to cool, diluted with an equal volume of ether (200 ml.), and freed from excess of acid by several washings with water. After drying, the solution of the crude reaction product in light petroleum was filtered through alumina and the residue obtained after evaporation of the solvent crystallised three times from chloroform-methyl alcohol. Yield, 75–85%.

isoLanostadiene forms lustrous needles, m. p. 146–148°, $[\alpha]_D + 66.4^\circ$ (c, 0.950), slightly Beilstein-positive, and giving a brown colouration with tetranitromethane (Wieland and Joost, *loc. cit.*, give m. p. 141–142° for cryptostadiene). It is soluble in chloroform, acetone, and ethyl acetate, sparingly soluble in methyl alcohol; like α -lanostadiene, and in contrast to the other members of the lanosterol group, it is sparingly soluble in hot glacial acetic acid (Found: C, 87.80; H, 12.18. Calc. for $C_{30}H_{50}$: C, 87.81; H, 12.19%). Ultra-violet absorption spectrum: maximum at 235 $m\mu$.

iso- γ -Lanostatriene.— γ -Lanosterol (6 g.; 1 mol.), dissolved in light petroleum (120 ml.; b. p. 60–80°) and treated with excess of phosphorus pentachloride (6 g.; 2 mols.) as described for *isolanostadiene*, gave good yields (60%) of iso- γ -lanostatriene, m. p. 130–132°, $[\alpha]_D + 11^\circ$ (c, 1.100), in colourless lustrous plates (Found: C, 88.14; H, 12.01. $C_{30}H_{48}$ requires C, 88.23; H, 11.76). Ultra-violet absorption spectrum: maxima at 235, 242, and 251 $m\mu$ ($E_{1\%}^{1cm} = 420, 450, \text{ and } 340$ respectively). Apart from higher intensities, the absorption curve was identical with that of γ -lanosteryl acetate.

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[Received, January 14th, 1947.]

280. Aliphatic Nitro-compounds. Part I. Preparation of Nitro-olefins by Dehydration of 2-Nitro-alcohols.*

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Nitroethylene and 1- and 2-nitroprop-1-ene are obtained in good yield by heating the appropriate nitro-alcohol with phthalic anhydride. The nitro-olefins are readily polymerised by alkali and decompose on heating; 2-nitroprop-1-ene decomposes rapidly even at room temperature.

ALTHOUGH β -nitrostyrene and its analogues have long been easily accessible, it is only within the last few years that satisfactory preparative methods for the purely aliphatic nitro-olefins have been described.

Four general methods are available all of which involve 2-nitroalkyl esters as intermediates: (a) reaction of olefins with nitrogen peroxide followed by treatment of the product with alkali (Levy and Scaife, *J.*, 1946, 1100), (b) treatment of 2-nitroalkyl esters with mild alkali (Schmidt and Rutz, *Ber.*, 1928, 61, 2142; Nightingale and Janes, *J. Amer. Chem. Soc.*, 1944, 66, 352), (c) pyrolysis of 2-nitroalkyl benzoates (Blomquist, Tapp, and Johnson, *J. Amer. Chem. Soc.*, 1945, 67, 1519), and (d) distillation of the 2-nitroalkyl acetates with a trace of sodium or potassium acetate (U.S.P. 2,257,980). The first two methods are not applicable to the preparation of nitroethylene and the nitropropenes owing to the ready polymerisation of the product.

The direct dehydration of nitro-alcohols to nitro-olefins, though well known in the case of 2-nitro-1-aryl alcohols, has hitherto been effected with only one aliphatic nitro-alcohol, 2-nitroethyl alcohol, which by treatment with potassium hydrogen sulphate gave a 50% yield of nitroethylene; this, however, cannot be used for more than a few grams of material at a time (Wieland and Sakellarios, *Ber.*, 1919, 52, 898).

Attempts to dehydrate 2-nitro-*n*-propyl alcohol with phosphoric oxide, potassium hydrogen sulphate, sulphuric acid, or zinc chloride failed to give any 2-nitropropene.

When the alcohol was heated with phthalic anhydride at 170° under a short column (to hold back unchanged material) at reduced pressure, a mixture of water and 2-nitroprop-1-ene

* Patent application pending.

(50—60% yield) distilled. 2-Nitroethyl and 2-nitroisopropyl alcohol under similar conditions gave nitroethylene and 1-nitroprop-1-ene respectively in 65—70% yield. The highest yields were obtained by using equimolecular parts of phthalic anhydride and nitro-alcohol, but, as the water formed distilled from the reactants, it was possible to reduce the anhydride to as little as 10 mol. %. Substituted phthalic anhydrides were equally effective.

Nitroethylene was obtained as a pale yellow lachrymatory oil which was moderately stable to heat and light but darkened slowly on keeping. It polymerised readily on treatment with water (cf. Wicland and Sakellarios, *loc. cit.*) and violently in presence of a trace of alkali. 2-Nitroprop-1-ene (Blomquist *et al.*, *loc. cit.*) was a pale yellow lachrymatory oil which rapidly turned green and decomposed to a black tar on being kept for a few days even in the dark; no means of arresting this decomposition was discovered. It decomposed vigorously on warming to 100° to give a complex mixture of products, and polymerised readily on treatment with alkalis. 1-Nitroprop-1-ene (Levy and Scaife, *loc. cit.*) resembled the two nitro-olefins described above, but was much more stable. It was apparently unchanged after one year's storage, and was unaffected by water, but polymerised vigorously on treatment with alkali, and decomposed on attempted distillation under atmospheric pressure.

EXPERIMENTAL.

Nitroethylene.—2-Nitroethyl alcohol (100 g.) (Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) and phthalic anhydride (180 g.) were mixed in a distillation apparatus fitted with a short fractionating column and heated by means of an oil-bath. The apparatus was evacuated to 80 mm. and the bath temperature maintained at 140—150° until the mixture was homogeneous. The bath temperature was then raised to 175° and held at 175—180° until distillation ceased. The distillate was dried (CaCl₂) and re-distilled, giving nitroethylene (55 g.; 66.5% theory) as a pale yellow oil, b. p. 38—39°/80 mm.

1-Nitroprop-1-ene.—2-Nitroisopropyl alcohol (105 g.) (Levy and Scaife, *loc. cit.*) was brought into reaction with phthalic anhydride (150 g.) at 180°/50 mm. as described above for 2-nitroethyl alcohol. 1-Nitroprop-1-ene was obtained as a pale yellow oil (58.5 g.; 67% theory), b. p. 54°/28 mm.

2-Nitroprop-1-ene.—2-Nitro-*n*-propyl alcohol (105 g.) (Vanderbilt and Hass, *Ind. Eng. Chem.*, 1940, 32, 34) was brought into reaction with phthalic anhydride (150 g.) at 175—180°/80 mm. as described above to give 2-nitroprop-1-ene as a pale yellow oil (48.5 g.; 55.5% theory), b. p. 58°/90 mm.

The authors wish to thank Dr. A. Lowe and Mr. R. H. Stanley for suggestions and assistance in carrying out this work, and Dr. N. Levy and Dr. H. A. Piggott for their interest and advice.

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HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9, AND BILLINGHAM, CO. DURHAM.

[Received, January 23rd, 1947.]

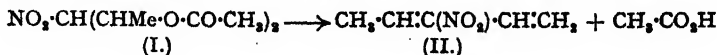
281. Aliphatic Nitro-compounds. Part II. Conjugated Nitro-dienes.

By G. D. BUCKLEY and (MRS.) J. L. CHARLISH.

Three conjugated nitro-dienes, *viz.*: 3-nitropenta-1 : 3-diene, 2-nitro-3-methylbuta-1 : 3-diene and 1-(1-nitrovinyl)cyclohexene have been synthesised. These compounds are very unstable, and preliminary experiments on their addition reactions have yielded no identifiable products. 1-(1-Nitrovinyl)cyclohexene readily forms a crystalline *dimeride* of unknown constitution.

IN view of the high reactivity of the α -nitro-olefins, it seemed likely that conjugated nitro-dienes, if they could be prepared, would form a useful starting point for novel synthesis. No attempt to prepare compounds of this type appears to be recorded in the literature, and it was therefore decided to apply to the problem the methods which are successful in the synthesis of the nitro-olefins.

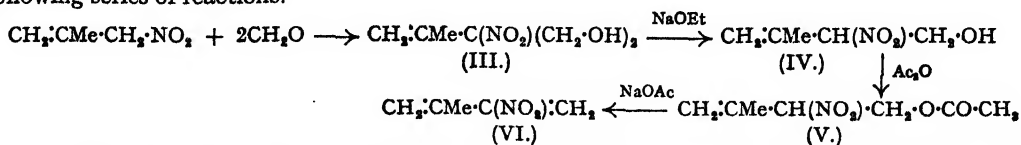
During the preparation of 2-nitroisopropyl acetate by acetylation of crude 2-nitroisopropyl alcohol formed by interaction of nitromethane and acetaldehyde (Henry, *Bull. Soc. chim.*, 1895, 13, 999), a large quantity of a high-boiling by-product was accumulated which on fractionation gave a mixture of diastereoisomerides of 3-nitro-2 : 4-diacetoxypentane (I), one of which was isolated in a pure crystalline state. On being heated with a small amount of sodium acetate, this material readily underwent fission to 3-nitropenta-1 : 3-diene (II) and acetic acid.



Like the simple nitro-olefins, the nitro-diene was a powerful lachrymator and very unstable. It decomposed to a black tar under the influence of light or heat, even in the presence of quinol, but was apparently unchanged after several weeks in the dark. It did not polymerise on treatment with alkalis but was readily polymerised by peroxides to a dark brown low-melting

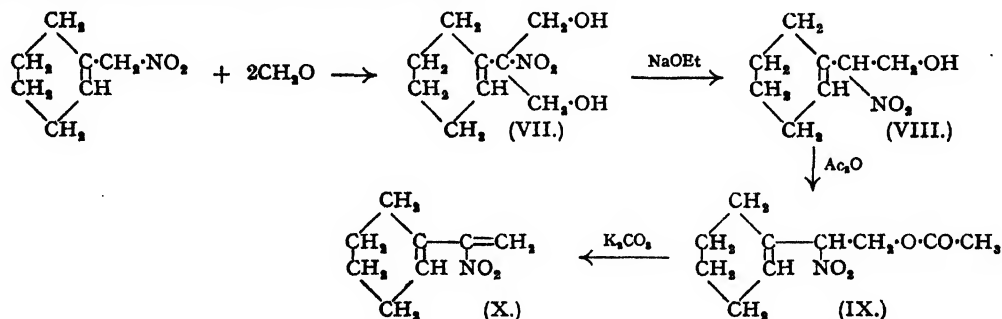
solid. It failed to react with aqueous sodium hydrogen sulphite and gave only tars on being warmed with maleic anhydride or cyclopentadiene. With bromine in carbon tetrachloride a dark oil was obtained which could not be purified; with piperidine an adduct was formed, but this was not further investigated.

2-Nitro-3-methylbuta-1:3-diene was prepared from 1-nitro-2-methylprop-2-ene by the following series of reactions.



The diol (III) on treatment with sodium ethoxide afforded the alcohol (IV) (cf. Schmidt and Wilkendorf, *Ber.*, 1919, 52, 389). Both the diol and the alcohol were difficult to purify, but for the preparation of (VI) this was immaterial, provided that the more stable acetate (V) was fractionated. The diene (VI) closely resembled the isomeric 3-nitropenta-1:3-diene in its properties but was even less stable, decomposing to a black tar on standing for a few days.

Application of these syntheses to 1-nitromethylcyclohexene gave 1-(1-nitro-2-acetoxyethyl)-cyclohexene (IX), but attempted distillation of this with sodium acetate resulted in violent decomposition. A similar result was obtained on attempting to dehydrate the alcohol (VIII) by distillation with 3-nitrophthalic anhydride.



By treating the nitro-ester (IX) in ether with potassium carbonate in presence of quinol a lachrymatory oil, presumably (X), was obtained, but this could not be purified. On standing it gave a solid which (from analysis and molecular weight) appeared to be a dimeride of (X). This product was also obtained directly if the potassium carbonate treatment was carried out in the absence of quinol. The yield was poor, but no other pure compounds were isolated. Although other new products were obtained, these could not be purified. Hydrogenation and addition of bromine to the dimer gave no definite products, and no systematic study of its reactions was attempted.

EXPERIMENTAL.

Microanalyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

3-Nitro-2:4-diacetoxypentane (I).—The high-boiling residue (700 g.) from a series of preparations of 2-nitroisopropyl acetate (prepared by acetylation of the crude nitro-alcohol from acetaldehyde and nitromethane; cf. Schmidt and Rutz, *Ber.*, 1928, 61, 2142) was fractionated to give a viscous yellow oil (490 g.), b. p. 140–150°/20 mm., which partly crystallised on standing. The solid compound was collected and recrystallised from light petroleum (b. p. 100–120°), forming colourless needles (40 g.), m. p. 85–86° (Found: C, 46.6; H, 5.95; N, 6.2. $\text{C}_9\text{H}_{15}\text{O}_5\text{N}$ requires C, 46.35; H, 6.4; N, 6.0%).

The liquid fraction was apparently essentially a mixture of the two diastereoisomerides (Found: C, 46.05; H, 6.25; N, 6.6%).

3-Nitropenta-1:3-diene (II).—Crude 3-nitro-2:4-diacetoxypentane (145 g.) was stirred with anhydrous sodium acetate (1 g.) at 95–100° for 1 hour and distilled under 12 mm. The distillate was washed thrice with saturated brine, dried, and fractionated to give 3-nitropenta-1:3-diene (38 g.; 54% theory) as a pale yellow lachrymatory oil, b. p. 63–65°/13 mm. (Found: C, 53.25; H, 6.3; N, 12.35. $\text{C}_5\text{H}_9\text{O}_2\text{N}$ requires C, 53.1; H, 6.2; N, 12.4%). A considerable tarry residue remained after the distillation.

2-Nitro-1-hydroxy-3-methyl-2-hydroxymethylbut-3-ene (III).—A mixture of 1-nitro-2-methylprop-2-ene (2 g.; Levy and Scaife, in the press), ethyl acetate (6 c.c.), paraformaldehyde (1.3 g.), and 33% aqueous potassium hydroxide (1 drop) was refluxed until all the paraformaldehyde had dissolved. The solution was kept at 0° for several days, and the crystalline precipitate collected and purified by recrystallisation from ethyl acetate, giving colourless rectangular prisms of the compound, m. p. 103–104° (Found: C, 44.75; H, 6.55; N, 8.5. $\text{C}_6\text{H}_{11}\text{O}_4\text{N}$ requires C, 44.7; H, 6.8; N, 8.7%).

2-Nitro-1-hydroxy-3-methylbut-3-ene (IV).—A mixture of 1-nitro-2-methylprop-2-ene (20 g.), isopropyl alcohol (60 c.c.), paraformaldehyde (13.2 g.), and 33% aqueous potassium hydroxide (6 drops) was refluxed for 3 hours. After cooling, a solution of sodium ethoxide [from sodium (5 g.) in alcohol (50 c.c.)] was added slowly with stirring below 10°. After 1 hour's stirring at 0–10°, the precipitate was collected, dissolved in a little water, acidified with dilute hydrochloric acid below 15°, saturated with salt, and extracted with ether. The extract was dried and fractionated to give the compound as a colourless oil (5.2 g.), b. p. 113–115°/15 mm. (Found: C, 45.55; H, 7.05; N, 10.1. $C_6H_{10}O_2N$ requires C, 45.8; H, 6.85; N, 10.7%); distillation was stopped at this point owing to incipient decomposition of the residue.

2-Nitro-1-acetoxy-3-methylbut-3-ene (V).—1-Nitro-2-methylprop-2-ene (24 g.) was converted into 2-nitro-1-hydroxy-3-methylbut-3-ene as described above. After removal of the ether, the crude product was mixed with acetic anhydride (25.2 g.), heated at 100° for 1 hour, and distilled to give the compound as a colourless oil (30.2 g.), b. p. 102–104°/0.5 mm. (Found: C, 49.2; H, 6.3; N, 7.8. $C_7H_{11}O_4N$ requires C, 48.6; H, 6.35; N, 8.1%).

2-Nitro-3-methylbuta-1:3-diene (VI).—2-Nitro-1-acetoxy-3-methylbut-3-ene (30 g.) and anhydrous sodium acetate (0.1 g.) were heated under 12 mm. (oil-bath temperature 110–120°). A colourless liquid distilled, but after a short time the residue began to decompose and distillation was stopped. The distillate was washed thrice with saturated brine, dried, and distilled to give 2-nitro-3-methylbuta-1:3-diene as a pale yellow lachrymatory oil (4.7 g.), b. p. 54–57°/14 mm. (Found: N, 12.3. $C_6H_8O_2N$ requires N, 12.4%). This closely resembled 3-nitropenta-1:3-diene in all its reactions.

1-(1-Nitro-2:2'-dihydroxyisopropyl)cyclohexene (VII).—1-Nitromethylcyclohexene (7 g.; Fraser and Kon, J., 1934, 604), paraformaldehyde (3.3 g.), ethyl acetate (25 c.c.), and 33% aqueous potassium hydroxide (3 drops) were refluxed until homogeneous (2 hours). The mixture was carefully neutralised with N-hydrochloric acid and the solvent removed under reduced pressure. After being kept in a desiccator for several days, the viscous residue crystallised to a white solid, m. p. 58–61°, which was very soluble in all organic solvents except light petroleum. Attempts to purify this material were unsuccessful.

1-(1-Nitro-2-hydroxyethyl)cyclohexene (VIII).—Crude 1-(1-nitro-2:2'-dihydroxyisopropyl)cyclohexene (9 g.) was dissolved in alcohol (25 c.c.) and treated with a solution of sodium ethoxide [from sodium (1.25 g.) in alcohol (15 c.c.)] below 15°. The mixture was then cooled to 0°, and the precipitated sodium salt collected, dissolved in water, and acidified with hydrochloric acid below 15°. The product was isolated by extraction with ether, dried, and distilled to give a pale yellow oil (3 g.; 38% theory), b. p. 98–100°/0.5 mm., which solidified to a crystalline mass of 1-(1-nitro-2-hydroxyethyl)cyclohexene, m. p. 45–46° (Found: C, 56.05; H, 7.25; N, 8.1. $C_8H_{13}O_2N$ requires C, 56.15; H, 7.6; N, 8.2%).

1-(1-Nitro-2-acetoxyethyl)cyclohexene (IX).—1-Nitromethylcyclohexene (21 g.), paraformaldehyde (9.9 g.), isopropyl alcohol (45 c.c.), and 33% aqueous potassium hydroxide (0.5 c.c.) were refluxed until a clear solution was obtained. After the solution had been cooled to 0°, a solution of sodium ethoxide [from sodium (3.75 g.) in alcohol (40 c.c.)] was added during 30 minutes. After 1 hour at 0–10° with stirring, the sodium salt was collected, dissolved in water (100 c.c.), and acidified with aqueous hydrochloric acid below 10°. The precipitated oil was extracted with ether, the extract dried, and the solvent removed. The crude product was cooled in ice, treated with 98% sulphuric acid (2 drops) followed by acetic anhydride (23 g.), and the mixture stirred at 60° for 2 hours. Distillation gave a colourless oil (22.5 g.), b. p. 102–105°/1 mm. (Found: N, 6.5. $C_{10}H_{15}O_4N$ requires N, 6.55%).

1-(1-Nitrovinyl)cyclohexene (X).—1-(1-Nitro-2-acetoxyethyl)cyclohexene (15 g.), potassium carbonate (15 g.), ether (50 c.c.), and quinol (0.1 g.) were refluxed with stirring for 4 hours, cooled, and washed with water. The ethereal solution was then treated with a further 0.1 g. of quinol and dried ($CaCl_2$). The ether was removed under reduced pressure at 30°, leaving a pale yellow lachrymatory oil (9.2 g.) which decomposed on attempted distillation under 0.5 mm. (Found: N, 8.8. $C_8H_{11}O_2N$ requires N, 9.15%). The nitro-diene did not react with aqueous sodium hydrogen sulphite and did not polymerise on boiling with dilute sodium carbonate solution; on keeping, it slowly dimerised.

1-(1-Nitrovinyl)cyclohexene Dimer.—1-(1-Nitro-2-acetoxyethyl)cyclohexene (48 g.), potassium carbonate (48 g.), and ether (150 c.c.) were refluxed with stirring for 4 hours, cooled, washed with water, and dried ($CaCl_2$). The ethereal solution was allowed to evaporate at 20° and the crystals were collected (9.9 g.) and washed with light petroleum (b. p. 100–120°). Recrystallisation from light petroleum and from acetic acid gave large colourless plates of 1-(1-nitrovinyl)cyclohexene dimer, m. p. 136–137° (Found: C, 62.6; H, 7.4; N, 9.3; *M* (cryoscopic in benzene), 290. $C_{16}H_{22}O_4N_2$ requires C, 62.75; H, 7.2; N, 9.15%; *M*, 306).

The authors wish to acknowledge the interest and advice of Dr. H. A. Piggott in this work.

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[Received, January 23rd, 1947.]

282. Aliphatic Nitro-compounds. Part III. Preparation of Alkyl 2-Nitroalkyl Ethers.*

By A. LAMBERT, C. W. SCAIFE, and A. E. WILDER-SMITH.

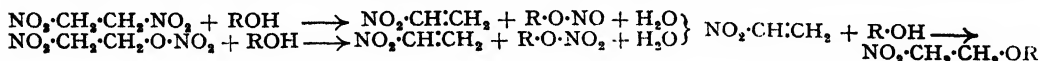
Alcohols add to α -nitro-olefins giving alkyl 2-nitroalkyl ethers, which on reduction yield amines, and on reaction with formaldehyde afford α -hydroxymethyl derivatives. 1:2-Dinitroethane (or 2-nitroethyl nitrate), 1:2-dinitropropane, and 1:2-dinitro-2-methyl-

* Cf. E.P.P. 573,872, 581,134.

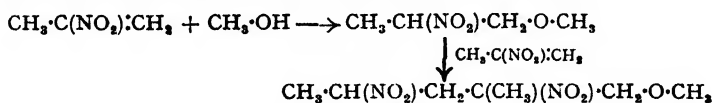
propane may be used as convenient substitutes for nitroethylene, 1-nitroprop-1-ene, and 1-nitro-2-methylprop-1-ene respectively.

THE addition of alcohols to some substituted nitro-olefins has been reported previously; thus, β -nitrostyrene (Rosenmund, *Ber.*, 1913, 46, 1034; Meisenheimer and Heim, *ibid.*, 1905, 38, 467), β -bromo- β -nitrostyrene (Thiele and Haeckel, *Annalen*, 1902, 325, 1), 2-nitro-1-(*p*-methoxyphenyl)prop-1-ene (Meisenheimer and Jochelson, *ibid.*, 1907, 355, 293), 1-bromo-1-nitrobut-1-ene and 1-bromo-1-nitropent-1-ene (Loevenich, Koch, and Pucknat, *Ber.*, 1930, 63, 636) all add alcohols in the presence of a basic catalyst to give 2-nitroalkyl ethers; benzylidene- ω -nitroacetophenone behaves similarly with boiling alcohol in the absence of a base (Wieland, *Annalen*, 1903, 328, 189; cf. Friedlander, Mahly, and Lazarus, *ibid.*, 1885, 229, 210, 234; Flürscheim, *J. pr. Chem.*, 1902, 66, 16). Since the present work was completed, the preparation of 2-nitroalkyl ethers by reaction of 1-nitrobut-1-ene and some higher nitro-olefins with sodium alkoxides has also been reported (U.S.P. 2,391,815).

The reaction of alcohols with 1 : 2-dinitro-paraffins and 2-nitroalkyl nitrates, obtained from the addition of nitrogen tetroxide to olefins (see Levy *et al.*, *J.*, 1946, 1096, 1100), and with α -nitro-olefins, was undertaken as part of a general investigation of the chemistry of these compounds and as a route to a wide variety of nitro- and amino-ethers. With boiling alcohols, 1 : 2-dinitroethane (or 2-nitroethyl nitrate) and 1 : 2-dinitropropane gave nitro-ethers as follows :



The reaction was found to be a general one, but yields diminished with increasing molecular weight of the alcohol and were lower with 2-nitroethyl nitrate than with 1 : 2-dinitroethane. Treatment of 1 : 2-dinitro-2-methylpropane with boiling alcohols gives 1-nitro-2-methylprop-1-ene which adds alcohols only in the presence of a basic catalyst. 2-Nitroprop-1-ene, 2-nitrobut-2-ene, and β -nitro- β -methylstyrene also require a basic catalyst, the highest yields being obtained by the use of an equivalent of the appropriate sodium alkoxide. In the reaction of 2-nitroprop-1-ene with sodium methoxide, in addition to methyl 2-nitro-*n*-propyl ether, some methyl 2 : 4-dinitro-2-methylamyl ether was obtained as a by-product, formed by addition of the mononitro-ether to 2-nitropropene (cf. Part VIII in this series) :



β -Nitrostyrene and sodium methoxide have been reported to give a small yield of methyl 2 : 4-dinitro-1 : 3-diphenylbutyl ether by a similar mechanism (Meisenheimer and Heim, *loc. cit.*). Nitroethylene was very reactive; even when stabilised with a small amount of phosphoric acid it added 2-methoxyethyl alcohol at ordinary temperature.

The nitro-ethers were readily hydrogenated to amines, and reaction with formaldehyde in the presence of a base gave α -hydroxymethyl derivatives.

The 2-nitrobut-2-ene used in this work was obtained from 2-nitro-3-acetoxybutane (Vanderbilt and Hass, *Ind. Eng. Chem.*, 1940, 32, 34) by heating it with sodium acetate (cf. Gen. Aniline and Film Corp., U.S.P. 2,257,980). Its structure was established by reduction with zinc and acetic acid (cf. Bouveault and Wahl, *Bull. Soc. chim.*, 1903, 29, 643) to methyl ethyl ketoxime. It is interesting that a product from the decomposition of the silver salt of nitroethane was described by Angeli and Alessandri (*Atti R. Accad. Lincei*, 1910, 19, 784; *Chem. Zentr.*, 1910, II, 731) as being probably 2-nitrobut-2-ene, but its structure was not proved.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton and Mr. A. E. Heron. All m. ps. are uncorrected.

Alkyl 2-Nitroalkyl Ethers.

(a) From 1 : 2-Dinitro-paraffins.—*Alkyl 2-nitroethyl ethers.* Methyl and ethyl 2-nitroethyl ethers were prepared by refluxing a 15% solution of 1 : 2-dinitroethane (Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) in the appropriate alcohol for 36 hours. The excess of alcohol was distilled, and the residual crude nitro-ether distilled first in steam at 60 mm. (to avoid the unstable residue formed on distillation) and then in high vacuum. For the higher alkyl 2-nitroethyl ethers, molten 1 : 2-dinitroethane was added to the boiling alcohol, the temperature of the bath being adjusted to distil off the alkyl nitrite as formed. The nitro-ether was then isolated by fractional distillation. The compounds prepared by this method are methyl (60% yield), b. p. 38°/1 mm., 67°/12 mm.; d_{20}^{20} 1.128; n_D^{20} 1.417 (Found : C, 34.7; H, 6.9; N, 13.4. $\text{C}_2\text{H}_5\text{O}_2\text{N}$ requires C, 34.3; H, 6.7; N, 13.3%); ethyl (50% yield), b. p. 46°/1 mm.;

72°/12 mm.; d_4^{25} 1.069 (Henry, *Rec. Trav. chim.*, 1899, 18, 259, records b. p. 178°/760 mm.; d_4^{25} 1.148) (Found: C, 40.5; H, 7.5; N, 12.0. Calc. for $C_6H_{11}O_2N$: C, 40.3; H, 7.6; N, 11.8%); *n*-propyl (45% yield), b. p. 48°/0.5 mm. (Found: N, 10.3. $C_6H_{11}O_2N$ requires N, 10.5%); isopropyl, b. p. 43°/0.5 mm. (Found: N, 10.6. $C_6H_{11}O_2N$ requires N, 10.5%); *n*-butyl (27% yield), b. p. 70—72°/2 mm. (Found: N, 9.7. $C_6H_{11}O_2N$ requires N, 9.5%); and *n*-amyl 2-nitroethyl ether (39% yield), b. p. 80—82°/1.5 mm. (Found: N, 8.4. $C_7H_{13}O_2N$ requires N, 8.7%).

Methyl nitro-tert.-butyl ether. 1:2-Dinitro-2-methylpropane (29.6 g.) (Levy and Scaife, in the press) in methyl alcohol (50 c.c.) was added dropwise with stirring during 30 minutes to a solution of sodium methoxide [from sodium (9.2 g.) in methyl alcohol (200 c.c.)]. The product after dilution with water and neutralisation (acetic acid) was extracted with ether and fractionated, giving *methyl nitro-tert.-butyl ether* (5.7 g.), b. p. 75°/15 mm. (Found: C, 45.1; H, 8.3; N, 10.8. $C_6H_{11}O_2N$ requires C, 45.1; H, 8.3; N, 10.5%).

Ethyl nitro-tert.-butyl ether. 1:2-Dinitro-2-methylpropane (29.6 g.), urea (6.0 g.), and alcohol (300 c.c.) were refluxed for 15 hours. Fractionation gave *ethyl nitro-tert.-butyl ether* (4.9 g.), b. p. 75°/15 mm. (Found: C, 48.7; H, 8.7; N, 9.3. $C_6H_{13}O_2N$ requires C, 49.0; H, 8.8; N, 9.5%). Some 1-nitro-2-methylprop-1-ene, b. p. 54—58°/11 mm., was also formed, and the alcohol recovered contained acetone, formed by hydrolysis of the dinitro-paraffin.

Methyl 2-nitroisopropyl ether. 1:2-Dinitropropane (30 g.) (Levy and Scaife, *J.*, 1946, 1100) was refluxed with methyl alcohol (70 g.) for 17 hours, and the mixture fractionated, giving *methyl 2-nitroisopropyl ether* (8 g.), b. p. 36—41°/1 mm., 62°/12 mm. (Found: C, 40.9; H, 7.7; N, 11.5. $C_4H_9O_2N$ requires C, 40.3; H, 7.6; N, 11.8%).

(b) *From Nitro-olefins*.—2-Nitro-2'-methoxydiethyl ether. A mixture of nitroethylene (19.7 g.), 2-methoxyethyl alcohol (100 c.c.), and orthophosphoric acid (1 c.c.), after being kept for 1 month at ordinary temperature, was distilled to give 2-nitro-2'-methoxydiethyl ether (12.5 g.), b. p. 81—84°/0.5 mm. (Found: C, 40.3; H, 7.3; N, 9.6. $C_4H_{11}O_2N$ requires C, 40.3; H, 7.4; N, 9.4%).

Methyl nitro-tert.-butyl ether. 1-Nitro-2-methylprop-1-ene (20.2 g.) was added dropwise with stirring during 30 minutes to a solution of an equivalent of sodium methoxide [from sodium (4.6 g.) in methyl alcohol (100 c.c.)] at ordinary temperature. The product, after dilution with water and neutralisation (acetic acid), was extracted with ether and distilled, giving *methyl nitro-tert.-butyl ether* (17.3 g.), b. p. 75°/15 mm.

2-Nitro-3-methoxybutane. This was prepared as described above from 2-nitrobut-2-ene (101 g.) and sodium methoxide in methyl alcohol. 2-Nitro-3-methoxybutane was obtained as a colourless liquid, b. p. 61—63°/15 mm. (Found: C, 45.1; H, 8.3. $C_6H_{11}O_2N$ requires C, 45.1; H, 8.3%). The 2-*p*-nitrophenylazo-derivative, from the sodium salt of the nitro-ether and *p*-nitrobenzenediazonium chloride, separated in two forms; α -form, fine yellow needles from light petroleum, m. p. 91° (Found: C, 46.6; H, 5.3; N, 19.7. $C_{11}H_{14}O_4N_4$ requires C, 46.8; H, 5.0; N, 19.8%), and β -form, red prisms from light petroleum, m. p. 84° (Found: C, 46.8; H, 5.1; N, 19.3%).

Methyl 2-nitropropyl ether. This was prepared from 2-nitroprop-1-ene (27 g.; see Part I of this series) and sodium methoxide in methyl alcohol as described above. Distillation gave *methyl 2-nitropropyl ether* (15.2 g.) as a colourless oil, b. p. 61—64°/14 mm. (Found: C, 40.6; H, 7.3. $C_4H_9O_2N$ requires C, 40.3; H, 7.6%). Some methyl 2:4-dinitro-2-methylamyl ether (4.8 g.), b. p. 92.5°/0.2 mm. (see Part VIII of this series), was also obtained.

Methyl 2-nitroisopropyl ether. Interaction of 1-nitroprop-1-ene (50 g.; see Part I of this series) with sodium methoxide in methyl alcohol as described above afforded methyl 2-nitroisopropyl ether (29 g.), b. p. 62°/12 mm., identical with that obtained from 1:2-dinitropropane.

2-Nitroisopropyl *n*-butyl ether. 1-Nitroprop-1-ene (25 g.) and a solution of sodium butoxide [from sodium (6.6 g.) in *n*-butyl alcohol (120 c.c.)], brought into reaction at 0—10° and worked up in the usual way, afforded 2-nitroisopropyl *n*-butyl ether (28 g.) as a colourless oil, b. p. 98—101°/14 mm. (Found: C, 52.7; H, 9.1; N, 8.6. $C_7H_{13}O_2N$ requires C, 52.2; H, 9.3; N, 8.7%).

Nitro-tert.-butyl *n*-amyl ether. 1-Nitro-2-methylprop-1-ene (50 g.) interacted with sodium *n*-amylate as described above to afford nitro-tert.-butyl *n*-amyl ether (26 g.), b. p. 75°/1 mm. (Found: C, 57.7; H, 9.9; N, 7.2. $C_9H_{19}O_2N$ requires C, 57.2; H, 10.0; N, 7.4%).

*Methyl 2-nitro-1-phenyl-*n*-propyl ether*. A solution of β -nitro- β -methylstyrene (489 g.; cf. Alles, *J. Amer. Chem. Soc.*, 1932, 54, 271) in dioxan (150 c.c.) was added to a solution of sodium methoxide [from sodium (10.35 g.) in methyl alcohol (150 c.c.)] at 10° during $\frac{1}{2}$ hour. After being stirred for 2 hours at room temperature, the mixture was diluted with water, acidified (acetic acid), extracted with ether, and distilled. Fractionation gave *methyl 2-nitro-1-phenyl-*n*-propyl ether* (51.3 g.) as a colourless oil, b. p. 138—141°/16 mm. (Found: C, 61.6; H, 6.5; N, 7.5. $C_{10}H_{13}O_2N$ requires C, 61.5; H, 6.6; N, 7.2%).

(c) *From 2-Nitroethyl Nitrate*.—2-Nitroethyl nitrate (30 g.) was refluxed with alcohol (150 c.c.) for 8 hours. Fractionation gave ethyl 2-nitroethyl ether (15 g.), b. p. 46°/1 mm.

Interaction of Nitroalkyl Ethers with Formaldehyde.

2-Nitro-3-methoxy-*n*-propyl Alcohol.—A solution of methyl 2-nitroethyl ether (26.25 g.) in alcohol (25 c.c.) was added to a solution of sodium hydroxide (10 g.) in alcohol (150 c.c.). Paraformaldehyde (7.5 g.) was added and the mixture stirred until a homogeneous solution was obtained. The sodium salt which separated was collected, dissolved in water, acidified (acetic acid), and extracted with ether. Distillation afforded 2-nitro-3-methoxy-*n*-propyl alcohol (13.5 g.), b. p. 99—104°/0.5 mm. (Found: C, 35.2; H, 6.8; N, 10.5. $C_4H_9O_4N$ requires C, 35.6; H, 6.7; N, 10.4%). Reduction of the nitro-alcohol with Adams's platinum catalyst in alcohol at 20°/100 atm. afforded methyl 2-aminoethyl ether, isolated as the *picrate*, m. p. 148—150° (Found: C, 35.9; H, 4.1. $C_2H_5ON, C_6H_5O_2N_3$ requires C, 35.6; H, 4.0%).

2-Nitro-2-methoxymethylpropane-1:3-diol.—Methyl 2-nitroethyl ether (9.32 g.) in methyl acetate (20 c.c.) was treated with paraformaldehyde (5.32 g.) and a trace of alcoholic potassium hydroxide.

After neutralisation the product was collected and crystallised from methyl acetate–light petroleum (b. p. 40–60°), giving 2-nitro-2-methoxymethylpropane-1 : 3-diol, m. p. 82.5–83.5° (Found : C, 36.2; H, 6.8; N, 8.4. $C_6H_{11}O_3N$ requires C, 36.4; H, 6.7; N, 8.5%). Reduction of the nitro-diol with Adams's platinum catalyst in alcohol gave 2-amino-2-methoxymethylpropane-1 : 3-diol, isolated as the *picrolonate*, m. p. 219–220° (Found : N, 17.6. $C_5H_{11}O_3N, C_{10}H_{19}O_6N_4$ requires N, 17.6%).

2-Nitro-2-ethoxymethylpropane-1 : 3-diol.—This was prepared from ethyl 2-nitroethyl ether as described above for the lower homologue. The diol was obtained as an undistillable oil, identified as the *di-p-nitrobenzoyl* derivative, m. p. 240–241° (Found : C, 50.7; H, 3.7; N, 8.3. $C_{20}H_{19}O_{11}N_4$ requires C, 50.4; H, 4.0; N, 8.8%).

2-Nitro-3-methoxy-2-methyl-n-butyl Alcohol.—A mixture of 2-nitro-3-methoxybutane (40 g.), paraformaldehyde (9.1 g.), aqueous sodium hydroxide (1.5 c.c. of 40%), and methyl alcohol (80 c.c.) was stirred overnight at ordinary temperature. After neutralisation with 2N-hydrochloric acid, distillation gave 2-nitro-3-methoxy-2-methyl-n-butyl alcohol (42 g.) as a colourless oil, b. p. 110°/15 mm., 82°/0.5 mm. (Found : C, 43.5; H, 7.7; N, 8.3. $C_8H_{15}O_3N$ requires C, 44.2; H, 7.9; N, 8.6%).

2-Nitro-3-n-butoxy-n-butyl Alcohol.—2-Nitroisopropyl n-butyl ether (53 g.) was dissolved in a solution of sodium hydroxide (13.5 g.) in water (100 c.c.) at 10°, and paraformaldehyde (10 g.) was added portionwise with stirring, the temperature being allowed to rise to 32°. After 20 minutes the solution was acidified (2N-hydrochloric acid), concentrated at 40–50° under reduced pressure, filtered, and distilled, giving 2-nitro-3-n-butoxy-n-butyl alcohol (53 g.) as a pale yellow oil, b. p. 98°/0.2 mm. (Found : C, 49.9; H, 9.2; N, 7.5. $C_8H_{17}O_3N$ requires C, 50.3; H, 8.9; N, 7.3%). Reduction of the nitro-alcohol (42 g.) in methyl alcohol (700 c.c.) with Raney nickel and hydrogen at 20°/68 atms. (initial pressure) gave 2-amino-3-n-butoxy-n-butyl alcohol (27 g.) as a colourless oil, b. p. 90–92°/0.1 mm. (Found : N, 9.1. $C_8H_{17}O_2N$ requires N, 8.7%).

Alkylaminoethyl Ethers.

Methyl 2-Aminoethyl Ether.—Methyl 2-nitroethyl ether (2.0 g.) in alcohol (22 c.c.) was hydrogenated with Adams's platinum catalyst at 20°/100 atms. to give methyl 2-aminoethyl ether, isolated as the *picrate*, m. p. 148–150° (Found : C, 35.9; H, 4.1. $C_4H_9ON, C_8H_9O_3N_3$ requires C, 35.6; H, 4.0%).

Ethyl 2-aminoethyl ether, obtained in 52% yield by similar reduction of ethyl 2-nitroethyl ether, had b. p. 105°; *picrolonate*, m. p. 208–209° (decomp.) (Found : C, 47.7; H, 5.5; N, 19.6. Calc. for $C_6H_{11}ON, C_{10}H_{19}O_3N_4$: C, 47.6; H, 5.4; N, 19.8%); *picrate*, m. p. 121–123° (Found : C, 37.2; H, 4.6; N, 17.8. Calc. for $C_4H_9ON, C_8H_9O_3N_3$: C, 37.6; H, 4.4; N, 17.6%). (Meyer, *Ber.*, 1905, **38**, 3130, records m. p. 204° and 122° respectively for these derivatives.)

2-Amino-3-methoxybutane.—2-Nitro-3-methoxybutane (20 g.) was added slowly with stirring to a mixture of iron powder (3.5 g.), ferric chloride (1 g.), concentrated hydrochloric acid (10 c.c.), and water (75 c.c.) at 100°. After being stirred at 100° for 15 hours, the mixture was basified strongly with aqueous sodium hydroxide and distilled in steam. The distillate was neutralised with hydrochloric acid, evaporated to dryness, basified with excess of 50% aqueous potassium hydroxide, and extracted with ether. The dried extract was fractionated, giving 2-amino-3-methoxybutane (5 g.) as colourless oil, b. p. 114–116° (Found : N, 13.3. $C_6H_{13}ON$ requires N, 13.6%). The *platinichloride* formed orange prisms from methyl alcohol–ether, m. p. 189–190° (decomp.) (Found : Pt, 31.1. $(C_6H_{13}ON)_3, H_4PtCl_6$ requires Pt, 31.6%); the 2 : 4-dinitrophenylurea (cf. McVeigh and Rose, *J.*, 1945, 621) formed yellow prisms from alcohol, m. p. 152–154° (Found : C, 45.9; H, 4.7; N, 17.6. $C_{12}H_{15}O_6N_4$ requires C, 46.1; H, 5.1; N, 17.9%). The same amine was formed in 50% yield by catalytic reduction of the nitro-ether with Raney nickel–methyl alcohol at 50°/120 atms.

2-Nitrobut-2-ene.—2-Nitro-3-acetoxybutane (161 g.; Vanderbilt and Hass, *loc. cit.*) was stirred with anhydrous sodium acetate (0.6 g.) at 100° for 1 hour and then distilled. The acidic distillate was washed successively with brine, aqueous sodium hydrogen carbonate, and brine, and the product fractionated, giving 2-nitrobut-2-ene (86 g.) as a pale yellow liquid, b. p. 55.5°/15 mm., n_D^{20} 1.4600 (Found : C, 46.9; H, 6.8; N, 13.8. $C_4H_7O_2N$ requires C, 47.5; H, 6.9; N, 13.8%). Reduction of the nitro-olefin (30 g.) with zinc and acetic acid (cf. Bouveault and Wahl, *loc. cit.*) gave methyl ethyl ketoxime (17 g.), b. p. 140–150°, which with 2 : 4-dinitrophenylhydrazine in hydrochloric acid gave methyl ethyl ketone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic specimen, 115°.

The authors wish to thank Mr. R. H. Stanley and Mr. H. Baldock for assistance with the preparative work, and Dr. N. Levy and Dr. H. A. Piggott for their interest and advice.

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[Received, January 23rd, 1947.]

283. Aliphatic Nitro-compounds. Part IV. Addition of Thiols to α -Nitro-olefins.*

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Thiols and hydrogen sulphide react with α -nitro-olefins under basic conditions, giving 2-nitroalkyl sulphides or thiols. The former can be oxidised to 2-nitroalkyl sulphones (also formed from the nitro-olefin and, e.g., sodium *p*-toluenesulphonate) or reduced to 2-aminoalkyl sulphides, which on oxidation give 2-aminoalkyl sulphones. In certain cases the 2-nitro-alcohols or their esters can be used as convenient substitutes for the nitro-olefins.

* Patent application pending.

As a logical extension of the synthesis of alkyl 2-nitroalkyl ethers by interaction of an α -nitro-olefin with an alcohol (see Part III of this series), the addition of thiols and hydrogen sulphide to nitro-olefins was investigated. This addition was found to be of wide application, and was more facile than the corresponding addition of alcohols.

In the presence of sodium methoxide, 2-nitroprop-1-ene and methylthiol gave an 86% yield of *methyl 2-nitropropyl sulphide*; similarly *methyl 2-nitro-1-methylpropyl sulphide* was obtained from 2-nitrobut-2-ene and methylthiol, *2-nitropropyl butyl sulphide* from 2-nitroprop-1-ene and butylthiol, *methyl 2-nitro-1-phenylethyl sulphide* from β -nitrostyrene and methylthiol, and *phenyl 2-nitroisopropyl sulphide* from 1-nitroprop-1-ene and thiophenol.

That thiols add to nitro-olefins with greater facility than do alcohols is well illustrated by the interaction of *n*-butylthiol with 2-nitroprop-1-ene; in the absence of a catalyst, this yielded 20% of 2-nitropropyl *n*-butyl sulphide, whilst only traces of methyl 2-nitropropyl ether are formed by refluxing methyl alcohol and the nitro-olefin; further, interaction of equimolecular proportions of sodium methoxide and 2-nitroprop-1-ene gave, in addition to the expected methyl 2-nitropropyl ether, some methyl 2 : 4-dinitro-2-methylamyl ether, formed by addition of the nitro-ether to unchanged nitro-olefin (cf. Part III of this series), but in the corresponding reaction with sodium thiomethoxide in place of sodium methoxide, this type of side reaction does not occur.

In the presence of piperidine as catalyst, nitro-*tert.*-butyl alcohol behaved as 1-nitro-2-methylprop-1-ene, and with butylthiol afforded *butyl nitro-tert.-butyl sulphide*; as in many examples cited in other parts of this series, 2-nitroethyl nitrate could be used as a convenient source of nitroethylene, and reacted with sodium thioalkoxides to give alkyl (or aryl) 2-nitroethyl sulphides. *Methyl, p-tolyl, p-n-butylphenyl, and carboxymethyl 2-nitroethyl sulphides* were prepared by this method, and sodium thiolacetate gave *2-nitroethyl thiolacetate*.

The addition of water to nitro-olefins in the presence of a basic catalyst is known to yield, in certain cases, 2-nitro-alcohols. It has been found that hydrogen sulphide reacts with nitro-olefins more readily than does water, and in the absence of catalysts, 2-nitrothiols are formed many of which react further with the nitro-olefin, giving di-(2-nitroalkyl) sulphides. The yields of thiol and sulphide vary widely from case to case, and are tabulated below.

Nitro-olefin.	Products and yield.
Nitroethylene	2-Nitroethylthiol (18%) and di-(2-nitroethyl) sulphide (48%)
2-Nitroprop-1-ene	2-Nitropropylthiol (7%)
1-Nitro-2-methylprop-1-ene	Nitro- <i>tert.</i> -butylthiol (31%) and di(nitro- <i>tert.</i> -butyl) sulphide (trace)
2-Nitrobut-2-ene	Di-(2-nitro-1-methylpropyl) sulphide (25%)
β -Nitrostyrene	Di-(2-nitro-1-phenylethyl) sulphide (37%)

The low yield of 2-nitropropylthiol obtained from 2-nitroprop-1-ene was due to the formation of much unstable high-boiling material. In the condensation of 2-nitrobut-2-ene with hydrogen sulphide, some thiol was formed but could not be obtained pure by distillation. The product from β -nitrostyrene was a mixture from which only one stereoisomeride of *di-(2-nitro-1-phenylethyl) sulphide* could be isolated.

In addition to their formation from nitroethylene and hydrogen sulphide, *2-nitroethylthiol* and *di-(2-nitroethyl) sulphide* were also obtained from 2-nitroethyl nitrate with potassium hydrogen sulphide and potassium sulphide respectively, and hydrolysis of 2-nitroethyl thiolacetate (from thiolacetic acid and 2-nitroethyl nitrate) also gave 2-nitroethylthiol in small yield. 1-Nitro-2-methylprop-1-ene and sodium sulphide gave *di(nitro-tert.-butyl) sulphide* and nitro-*tert.*-butylthiol.

Oxidation of nitroalkyl sulphides with hydrogen peroxide in acetic acid afforded the nitroalkyl sulphones in good yield. Thus, *p*-tolyl 2-nitroethyl sulphide gave *p-tolyl 2-nitroethyl sulphone*, which is also obtained by reaction of sodium *p*-toluenesulphinate with 2-nitroethyl nitrate or nitroethylene. Catalytic reduction (Raney nickel) of the nitro-sulphones yielded amino-sulphones, and these were also formed by similar reduction of the nitroalkyl sulphides to aminoalkyl sulphides, followed by oxidation with hydrogen peroxide.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

Methyl 2-Nitro-1-methylpropyl Sulphide.—A solution of sodium methoxide (from sodium (9.6 g.) in methyl alcohol (100 c.c.)) was added slowly with stirring to a solution of methylthiol (24 g.) in methyl alcohol (60 c.c.) at -5° . 2-Nitrobut-2-ene (42 g.; see Part III of this series) was then added dropwise during 40 minutes with stirring at $0-5^{\circ}$, and, after being stirred for a further hour, the solution was poured into ice-water (400 c.c.), acidified with dilute acetic acid, and extracted with ether. Fractionation

of the dried extract gave *methyl 2-nitro-1-methylpropyl sulphide* (26 g.) as a colourless unpleasant smelling oil, b. p. 91—96°/15 mm. (Found : N, 9.1. $C_5H_{11}O_2NS$ requires N, 9.4%).

Methyl 2-Nitropropyl Sulphide.—2-Nitroprop-1-ene (30 g.; Part I of this series) was brought into reaction with methylthiol (20 g.) as described above. *Methyl 2-nitropropyl sulphide* (40 g.) was obtained as a colourless liquid, b. p. 98—100°/16 mm. (Found : N, 10.2. $C_4H_9O_2NS$ requires N, 10.4%).

Methyl 2-Nitropropyl Sulphone.—Hydrogen peroxide (30%; 45 c.c.) was added quickly with shaking to a boiling solution of methyl 2-nitropropyl sulphide (10 g.) in glacial acetic acid (40 c.c.). The mixture was boiled for 1 hour and evaporated to dryness under reduced pressure at 40—50°. Crystallisation of the residue from benzene gave *methyl 2-nitropropyl sulphone*, m. p. 69—70° (Found : C, 28.8; H, 5.1; N, 7.9. $C_4H_9O_4NS$ requires C, 28.7; H, 5.4; N, 8.4%).

Methyl 2-Aminopropyl Sulphone.—Methyl 2-nitropropyl sulphone (12 g.) in methyl alcohol (600 c.c.) was shaken with Raney nickel and hydrogen (75 atms. initial pressure) at room temperature. Distillation of the product gave methyl 2-aminopropyl sulphone (2 g.) as a viscous pale yellow oil, b. p. 110—120°/0.3 mm.; the residue decomposed. The benzoyl derivative formed colourless needles from ethyl acetate, m. p. 154° (Found : N, 5.9; S, 13.9. $C_{11}H_{15}O_3NS$ requires N, 5.8; S, 13.3%).

Phenyl 2-Nitroisopropyl Sulphide.—Thiophenol (10 g.) was added to a solution of sodium (2.1 g.) in methyl alcohol (50 c.c.) at 0°. 1-Nitroprop-1-ene (7.9 g.; Part I of this series) was added dropwise with stirring at 0—5° and the product treated as described above for the preparation of methyl 2-nitro-1-methylpropyl sulphide. *Phenyl 2-nitroisopropyl sulphide* (11.5 g.) was obtained as a colourless liquid, b. p. 110—111°/0.1 mm. (Found : N, 6.9. $C_9H_{11}O_2NS$ requires N, 7.1%).

Methyl 2-Nitro-1-phenylethyl Sulphide.—A solution of sodium methoxide [from sodium (9.2 g.) in methyl alcohol (100 c.c.)] was added slowly with stirring to a solution of methylthiol (21 g.) in methyl alcohol at —10°. A solution of β -nitrostyrene (29.8 g.) in dioxan (500 c.c.) was then added dropwise with stirring during $\frac{1}{2}$ hour at 10°. After being stirred at room temperature for $\frac{1}{2}$ hour, the mixture was poured into water and extracted with ether. Distillation of the dried ethereal extract gave *methyl 2-nitro-1-phenylethyl sulphide* (19.1 g.) as a yellow oil, b. p. 168—172°/22 mm. (Found : N, 6.7. $C_9H_{11}O_2NS$ requires N, 6.9%).

2-Nitropropyl Butyl Sulphide.—Butylthiol (10.4 g.) was added to a solution of sodium (2.7 g.) in methyl alcohol (50 c.c.) at 0°. 2-Nitroprop-1-ene (10 g.) was then added dropwise with stirring at 0—10° and the product isolated in the usual way. *2-Nitropropyl butyl sulphide* (12 g.) was obtained as a colourless liquid, b. p. 124—128°/13 mm. (Found : N, 7.8. $C_7H_{15}O_2NS$ requires N, 7.9%). The same product was also obtained by interaction of *n*-butylthiol and 2-nitroprop-1-ene in absence of a catalyst. Equimols. of the reactants were warmed in methyl alcohol solution until reaction commenced, heating was discontinued, and the mixture kept for 12 hours, diluted with ether, washed with sodium hydrogen carbonate and with water, and finally distilled, giving 2-nitropropyl butyl sulphide, b. p. 120—130°/16 mm. in 19% yield. Identity was established by oxidation to the sulphone (see below).

2-Nitropropyl Butyl Sulphone.—Prepared from the sulphide by oxidation with hydrogen peroxide in glacial acetic acid, the sulphone separated from methyl alcohol in colourless plates, m. p. 36—37° (Found : N, 6.2; S, 14.7. $C_8H_{15}O_4NS$ requires N, 6.7; S, 15.3%).

n-Butyl Nitro-tert.-butyl Sulphide.—A mixture of *n*-butylthiol (7.0 g.), nitro-*tert.*-butyl alcohol (10 g.; see Part XVIII of this series), and piperidine (1 g.) was kept at 20° for 3 days. The mixture was neutralised with 2*N*-hydrochloric acid, diluted with ether, and washed with water. Distillation of the ethereal solution gave *n-butyl nitro-tert.-butyl sulphide* (8.6 g.) as a colourless liquid, b. p. 124°/11 mm. (Found : C, 50.4; H, 8.6; N, 7.2. $C_8H_{17}O_2NS$ requires C, 50.3; H, 8.9; N, 7.3%).

m-Di(nitro-tert.-butylsulphonyl)benzene.—Dithioresorcinol (14.2 g.) was added with stirring to a solution of sodium methoxide [from sodium (4.6 g.) in methyl alcohol (160 c.c.)] at 0—10°. 1-Nitro-2-methylprop-1-ene (20.2 g.; Levy and Scaife, in the press) was added dropwise at 0—5°, and the mixture stirred at room temperature for a further 2 hours. The product was poured into ice-water, acidified with dilute acetic acid, and extracted with ether. Distillation of the ethereal extract gave a colourless oil (18.1 g.), b. p. 130°/0.5 mm. The sulphur content of this oil (Found : S, 24.7. Calc. for $C_{14}H_{20}O_4N_2S_2$: S, 18.6%) indicated that it was contaminated with dithioresorcinol. However, on oxidation with hydrogen peroxide in glacial acetic acid pure *m-di(nitro-tert.-butylsulphonyl)benzene* was obtained in 17% yield. It separated from methyl alcohol in colourless needles, m. p. 166—168° (Found : N, 7.1. $C_{14}H_{20}O_4N_2S_2$ requires N, 6.9%).

Methyl 2-Nitroethyl Sulphide.—A solution of methylthiol (9.6 g.) in methyl alcohol (50 c.c.) was added to a solution of sodium methoxide (10.8 g.) in methyl alcohol (30 c.c.) at —10°. 2-Nitroethyl nitrate (27.2 g.; Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) was added dropwise with stirring at —5°, and, after being stirred for 3½ hours at 0°, the solution was filtered and distilled, giving *methyl 2-nitroethyl sulphide*, b. p. 105°/20 mm., in 80% yield (Found : C, 30.2; H, 5.8; N, 11.1. $C_3H_7O_2NS$ requires C, 29.8; H, 5.8; N, 11.6%).

Methyl 2-Aminoethyl Sulphide.—Methyl 2-nitroethyl sulphide (40 g.) in methyl alcohol (700 c.c.) was hydrogenated over Raney nickel at 50—60° and 100 atms. (initial pressure). Fractionation of the product gave methyl 2-aminoethyl sulphide (20 g.) as a colourless liquid, b. p. 90—91°/114 mm. (Schneider, *Annalen*, 1912, 386, 337, gives b. p. 146—148°/760 mm.). The picrate had m. p. 119° (Schneider, *loc. cit.*, gives m. p. 119°).

Methyl 2-Nitroethyl Sulphone.—Oxidation of methyl 2-nitroethyl sulphide (12.1 g.) with hydrogen peroxide in boiling glacial acetic acid gave *methyl 2-nitroethyl sulphone* (12.1 g.), colourless needles from alcohol, m. p. 78° (Found : C, 23.3; H, 5.1; N, 9.1. $C_3H_7O_4NS$ requires C, 23.5; H, 4.6; N, 9.1%).

Methyl 2-Aminoethyl Sulphone.—Methyl 2-nitroethyl sulphone (3.06 g.) in methyl alcohol (40 c.c.) was hydrogenated (Raney nickel) at ordinary temperature and pressure. Distillation of the product gave *methyl 2-aminoethyl sulphone* as a colourless liquid, b. p. 180°/0.02 mm., in almost quantitative yield (Found : N, 10.9. $C_3H_7O_4NS$ requires N, 11.4%). The hydrochloride had m. p. 168° (Schneider, *loc. cit.*, gives m. p. 169°), and the benzoyl derivative, m. p. 134° (Schneider, *loc. cit.*, gives m. p. 134°).

p-n-Butylphenyl 2-Nitroethyl Sulphone.—2-Nitroethyl nitrate (16.4 g.) was added dropwise to a stirred solution of sodium thio-*p*-butylphenol (22.6 g.) in methyl alcohol (200 c.c.) at —10° to —5°.

After being stirred for 4 hours the mixture was filtered, evaporated to dryness, and extracted with ether. Removal of the ether gave crude *p*-*n*-butylphenyl 2-nitroethyl sulphide as a colourless syrup which on oxidation with hydrogen peroxide gave *p*-*n*-butylphenyl 2-nitroethyl sulphone as colourless needles from alcohol, m. p. 91–92° (Found: C, 53.1; H, 6.4; N, 5.3. $C_{15}H_{17}O_4NS$ requires C, 53.1; H, 6.3; N, 5.2%).

Carboxymethyl 2-Nitroethyl Sulphide.—To a solution of thioglycolic acid (9.2 g.) and sodium methoxide (10.8 g.) in methyl alcohol (150 c.c.), 2-nitroethyl nitrate (13.6 g.) was added dropwise with stirring at 0–5°. After being stirred for 3 hours at 0–20° the mixture was filtered, treated with 2*N*-hydrochloric acid (50 c.c.), evaporated to dryness, and extracted with ether. Removal of the ether gave *carboxymethyl 2-nitroethyl sulphide* (9.9 g.) as a colourless syrup which solidified on standing, and crystallised from toluene, m. p. 47° (Found: C, 29.4; H, 4.0; N, 8.5. $C_4H_7O_4NS$ requires C, 29.1; H, 4.2; N, 8.5%).

Carboxymethyl 2-Nitroethyl Sulphone.—Oxidation of *carboxymethyl 2-nitroethyl sulphide* with hydrogen peroxide in boiling glacial acetic acid gave *carboxymethyl 2-nitroethyl sulphone* in almost quantitative yield. From alcohol-ether-light petroleum (b. p. 40–60°), white crystals, m. p. 115–116°, were obtained (Found: C, 24.7; H, 3.9; N, 7.1. $C_4H_7O_6NS$ requires C, 24.4; H, 3.6; N, 7.1%). The *ethyl ester*, prepared in almost quantitative yield by heating the acid in alcoholic solution, formed colourless crystals from alcohol, m. p. 62° (Found: C, 32.2; H, 4.8; N, 6.3. $C_6H_{11}O_6NS$ requires C, 32.0; H, 4.8; N, 6.2%).

Carboxymethyl 2-Aminoethyl Sulphide.—*Carboxymethyl 2-nitroethyl sulphide* (8.0 g.) in methyl alcohol (200 c.c.) was hydrogenated over Raney nickel at ordinary temperature and pressure. After filtration, removal of the methyl alcohol gave a nickel salt, which was dissolved in water and decomposed by hydrogen sulphide. The solution was filtered from nickel sulphide and evaporated to dryness. Crystallisation of the residue from alcohol gave *carboxymethyl 2-aminoethyl sulphide* (2.8 g.), m. p. 156° (Found: C, 35.3; H, 5.5; N, 10.6. $C_4H_9O_2NS$ requires C, 35.5; H, 6.6; N, 10.3%).

2-Nitroethyl Thiocacetate.—To a solution of thiocetic acid (15.2 g.) and sodium methoxide (10.8 g.) in methyl alcohol (200 c.c.), 2-nitroethyl nitrate (27.2 g.) was added dropwise with stirring at 0–5°. After being stirred for 2 hours, the filtered solution was evaporated and distilled, giving *2-nitroethyl thiocacetate* (23.1 g.), b. p. 68–70°/0.1 mm. (Found: C, 32.0; H, 5.4; N, 9.4. $C_4H_7O_3NS$ requires C, 32.2; H, 4.7; N, 9.4%).

2-Nitroethylthiol.—(a) *From nitroethylene and hydrogen sulphide.* Nitroethylene (20 g.; Part I of this series) was added slowly with stirring to a saturated solution of hydrogen sulphide in alcohol (350 c.c.) at 0°. The vessel was then sealed and kept at 20° for 2 hours; some di-(2-nitroethyl) sulphide separated at this stage. After removal of the alcohol, distillation of the residue in nitrogen gave *2-nitroethylthiol* (5.2 g.) as a colourless liquid, b. p. 86–87°/14 mm. (Found: C, 22.4; H, 4.3; N, 12.9; S, 29.5. $C_4H_7O_2NS$ requires C, 22.4; H, 4.7; N, 13.1; S, 29.9%), and *di-(2-nitroethyl) sulphide* (11.8 g.) as a pale yellow oil, b. p. 140–144°/0.2 mm., which darkened on standing (Found: S, 17.8. $C_6H_9O_4N_2S$ requires S, 17.8%).

(b) *From 2-nitroethyl nitrate and potassium hydrogen sulphide.* 2-Nitroethyl nitrate (13.6 g.) was added dropwise with stirring to a solution of potassium hydrogen sulphide (7.2 g.) in methyl alcohol (100 c.c.) at room temperature. After being stirred for 3 hours, the mixture was filtered, evaporated to dryness, and extracted with ether. Distillation of the ethereal solution gave *2-nitroethylthiol* (2.1 g.), b. p. 95°/20 mm.

(c) *By hydrolysis of 2-nitroethyl thiocacetate.* 2-Nitroethyl thiocacetate (7.4 g.) was kept for 1 hour at 20° with a solution of sodium hydroxide (4 g.) in water (70 c.c.). The solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution, washed free of acetic acid with aqueous sodium hydrogen carbonate, was distilled in nitrogen, giving *2-nitroethylthiol* (0.5 g.), b. p. 95–100°/20 mm. Mercury 2-nitrothioethoxide, prepared from the thiol and mercuric cyanide in alcohol, separated from alcohol in colourless needles, m. p. 67–68°. It decomposed rapidly on standing. *2:4-Dinitrophenyl 2-nitroethyl sulphide* was prepared by addition of 1-chloro-2:4-dinitrobenzene (1.1 g.) in alcohol (20 c.c.) to a solution of the thiol (0.6 g.) in *N*-sodium hydroxide (5.5 c.c.). The solution was heated to boiling and the product which separated crystallised from benzene, m. p. 196–197° (Found: N, 15.6. $C_8H_9O_6N_3S$ requires N, 15.4%).

Di-(2-nitroethyl) Sulphide.—2-Nitroethyl nitrate (27.2 g.) was added dropwise to a stirred solution of potassium sulphide (11.0 g.) in methyl alcohol (200 c.c.) at 0–5°. After being stirred for 2 hours, the filtered solution was evaporated to dryness, the residue extracted with acetone, and the extract distilled, yielding *di-(2-nitroethyl) sulphide* (9 g.) identical with that obtained from nitroethylene and hydrogen sulphide. Oxidation of the samples with hydrogen peroxide gave identical specimens of *di-(2-nitroethyl) sulphone*, colourless plates from acetone, m. p. 132° (Found: C, 22.6; H, 3.7; N, 13.2. $C_6H_9O_4N_2S$ requires C, 22.6; H, 3.8; N, 13.2%).

Nitro-tert.-butylthiol and Di(nitro-tert.-butyl) Sulphide.—(a) *From sodium sulphide.* 1-Nitro-2-methylprop-1-ene (101 g.) was added slowly to a stirred solution of sodium sulphide ($Na_2S \cdot 9H_2O$; 120 g.) in water (450 c.c.) at 0–10°. When homogeneous, the solution was treated with acetic acid (120 c.c. of 50%) and extracted with ether. Distillation afforded a fraction, b. p. 46–64°/7 mm. (38 g.), from which unchanged nitro-olefin was extracted with aqueous sodium hydrogen sulphite, giving *nitro-tert.-butylthiol* (12 g.), b. p. 58–63°/7 mm. (Found: C, 35.9; H, 6.3; N, 11.0; S, 22.9. $C_4H_9O_2NS$ requires C, 35.6; H, 6.7; N, 10.4; S, 23.7%). Mercury nitro-tert.-thiobutoxide, colourless needles from alcohol, m. p. 108°, decomposes slowly on keeping. The residue, after removal of the fraction, b. p. 46–64°/7 mm., was crystallised from benzene-light petroleum to give *di(nitro-tert.-butyl) sulphide*, m. p. 59–60° (Found: C, 40.8; H, 6.8; S, 13.5. $C_8H_{15}O_4N_2S$ requires C, 40.7; H, 6.8; S, 13.6%).

(b) *From hydrogen sulphide.* A solution of 1-nitro-2-methylprop-1-ene (20 g.) in alcohol (350 c.c.) was saturated at 0° with hydrogen sulphide and kept in a sealed vessel for 7 days at 20°. The alcohol was distilled and the residue, after extraction with aqueous sodium hydrogen sulphite, was isolated with ether and distilled giving *nitro-tert.-butylthiol* (8.4 g.), b. p. 68°/8 mm., and a residue (0.5 g.) which, after crystallisation from benzene-light petroleum, afforded *di(nitro-tert.-butyl) sulphide*, m. p. 59–60°.

Di(nitro-tert.-butyl) Sulphone.—Oxidation of di(nitro-tert.-butyl) sulphide with hydrogen peroxide in the manner described above gave di(nitro-tert.-butyl) sulphone, long colourless needles from methyl alcohol, m. p. 186° (Found: N, 10.4. $C_8H_{16}O_6N_2S$ requires N, 10.4%).

Di-(2-nitro-1-methylpropyl) Sulphide.—A solution of 2-nitrobut-2-ene (27.4 g.) in alcohol (350 c.c.) was saturated with hydrogen sulphide at 0°. The vessel was then sealed and kept at room temperature for 16 hours. After filtration and removal of the alcohol, distillation of the residue in a stream of nitrogen gave an almost colourless liquid, b. p. 70–90°/15 mm., and di-(2-nitro-1-methylpropyl) sulphide (3 g.), b. p. 110°/0.04 mm. (Found: S, 13.4. $C_8H_{16}O_4N_2S$ requires S, 13.6%). The fraction, b. p. 70–90°/15 mm., appeared to be a mixture of unchanged nitro-olefin and the stereoisomerides of 2-nitro-1-methylpropylthiol, but attempts to separate them by distillation failed. Redistillation of this material after 2 weeks, however, gave more (5 g.) di-(2-nitro-1-methylpropyl) sulphide, indicating reaction between the components.

Di-(2-nitro-1-methylpropyl) Sulphone.—Oxidation of the crude sulphide with hydrogen peroxide in the usual way gave a mixture of stereoisomerides of di-(2-nitro-1-methylpropyl) sulphone which separated from benzene–light petroleum (b. p. 60–80°) in colourless needles, m. p. 92–98° (Found: C, 35.8; H, 6.0; N, 10.2. $C_8H_{16}O_6N_2S$ requires C, 35.8; H, 6.0; N, 10.4%).

2-Nitropropylthiol.—2-Nitroprop-1-ene (20 g.) was added slowly with stirring to a saturated solution of hydrogen sulphide in alcohol (350 c.c.) at 0°. The vessel was then sealed and kept at 20° for 1½ hours. After removal of the alcohol, distillation of the residue gave 2-nitropropylthiol (2 g.) as a colourless liquid, b. p. 83°/12 mm. (Found: S, 25.8. $C_3H_7O_2NS$ requires S, 26.4%). The dark residue decomposed on attempted distillation at 0.2 mm.

Di-(2-nitro-1-phenylethyl) Sulphide.—A solution of β -nitrostyrene (30 g.) in alcohol (350 c.c.) was saturated with hydrogen sulphide at 0°. The vessel was then sealed and kept at 20° for 2 hours. On cooling to 0°, di-(2-nitro-1-phenylethyl) sulphide (9.5 g.) separated as a colourless solid which crystallised from alcohol in large prisms, m. p. 106–107° (Found: N, 8.3; S, 9.5. $C_{16}H_{16}O_4N_2S$ requires N, 8.4; S, 9.6%). The bulk of the product remained in the mother liquors as a viscous oil, b. p. 80–120°/0.08 mm.; this mixture of stereoisomerides was not separated.

p-Tolyl 2-Nitroethyl Sulphone.—(a) *From nitroethylene*. Nitroethylene (3.7 g.) was added slowly to a stirred solution of sodium *p*-toluenesulphinate (8.9 g.) in water (25 c.c.) at 0°. After being stirred at 0° for 3 hours, the mixture was filtered from polynitroethylene, acidified with acetic acid, and extracted with ether. Concentration of the ethereal solution gave *p*-tolyl 2-nitroethyl sulphone (0.6 g.) as colourless needles, m. p. 114° (from alcohol) (Found: C, 46.8; H, 5.0; N, 6.6. $C_9H_{11}O_4NS$ requires C, 47.2; H, 4.8; N, 6.1%).

(b) *From 2-nitroethyl nitrate and sodium p-toluenesulphinate*. 2-Nitroethyl nitrate (13.6 g.) was added dropwise to a stirred solution of sodium *p*-toluenesulphinate (17.8 g.) in water (50 c.c.) at 20°. The product was filtered off and crystallised from alcohol, giving *p*-tolyl 2-nitroethyl sulphone (18.3 g.), m. p. and mixed m. p. 114°.

(c) *From p-tolyl 2-nitroethyl sulphide*. A solution of sodium methoxide [from sodium (2.3 g.) in methyl alcohol (50 c.c.)] was added to a solution of thio-*p*-cresol (12.4 g.) in methyl alcohol (100 c.c.) at 0°. 2-Nitroethyl nitrate (13.6 g.) was then added dropwise with stirring at –10° to –5°. After being stirred for 3 hours the filtered solution was evaporated, giving crude *p*-tolyl 2-nitroethyl sulphide as a colourless oil, which on oxidation with hydrogen peroxide in acetic acid gave *p*-tolyl 2-nitroethyl sulphone (21 g.), m. p. and mixed m. p. 114°.

p-Tolyl 2-Aminoethyl Sulphone.—*p*-Tolyl 2-nitroethyl sulphone (2.3 g.) in methyl alcohol (40 c.c.) was hydrogenated over Raney nickel at ordinary temperature and pressure. Evaporation of the filtered solution gave *p*-tolyl 2-aminoethyl sulphone as a colourless syrup. The benzoyl derivative had m. p. 158° (Found: C, 63.2; H, 5.7; N, 4.7. $C_{16}H_{17}O_2NS$ requires C, 63.3; H, 5.6; N, 4.6%).

p-Tolyl 2-Aminoethyl Sulphide.—Crude *p*-tolyl 2-nitroethyl sulphide (5 g.) in methyl alcohol (50 c.c.) was hydrogenated over Raney nickel at ordinary temperature and pressure. Removal of the methyl alcohol gave a colourless syrup, which with ethereal hydrogen chloride yielded *p*-tolyl 2-aminoethyl sulphide hydrochloride (4.1 g.), colourless crystals from alcohol-ether, m. p. 132° (Found: C, 53.3; H, 6.9; N, 6.8. $C_9H_{13}NS.HCl$ requires C, 53.1; H, 6.9; N, 6.9%).

The authors wish to acknowledge the interest and advice of Dr. H. A. Piggott and Mr. J. D. Rose in this work.

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[Received, January 23rd, 1947.]

284. Aliphatic Nitro-compounds. Part V. Preparation of 2-Nitroalkanesulphonic Acids by Interaction of α -Nitro-olefins and Sodium Hydrogen Sulphite.*

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α -Nitro-olefins react with sodium hydrogen sulphite giving sodium 2-nitroalkanesulphonates, which on catalytic reduction afford the corresponding 2-aminoalkanesulphonic acids in good yield. In the absence of oxygen, sulphurous acid can be used in place of sodium hydrogen sulphite, and in many cases esters of 2-nitro-alcohols (2-nitroethyl nitrate, 2-nitropropyl acetate) behave in the same way as the nitro-olefins.

* Cf. E.P. 571,157.

THE interaction of α -nitro-olefins and sodium hydrogen sulphite was studied during a general investigation of the addition reactions of nitro-olefins, as a potentially interesting route to certain 2-aminoalkanesulphonic acids required as intermediates in the synthesis of dyestuffs.

The addition of alkali hydrogen sulphites to unsaturated substances has been studied by many workers. Rosenthal (*Annalen*, 1886, 233, 38) prepared the diammonium salt of β -sulphopropionic acid by the interaction of ammonium hydrogen sulphite and ammonium acrylate. The addition of potassium hydrogen sulphite to allyl alcohol was demonstrated by Müller (*Ber.*, 1873, 6, 1442), and the product was established by Marckwald (*ibid.*, 1898, 31, 1864) as potassium 1-hydroxypropane-3-sulphonate. Kolker and Lapworth (*J.*, 1925, 307) added ammonium hydrogen sulphite to a large number of olefins, whilst the reaction of sodium hydrogen sulphite and styrene, first reported by Ashworth and Burkhardt (*J.*, 1928, 1791), has been shown by Kharasch, Schenck, and Mayo (*J. Amer. Chem. Soc.*, 1939, 61, 3092) to yield 2-phenylethane-1-sulphonic acid, 2-phenylethylene-1-sulphonic acid, 2-phenylethane-1:1-disulphonic acid, and 2-hydroxy-2-phenylethane-1-sulphonic acid. Knoevenagel and Morrisse (*Ber.*, 1904, 37, 4038) successfully added alkali hydrogen sulphites to $\alpha\beta$ -unsaturated aldehydes and ketones, and the addition to unsaturated furyl compounds has been described by the American Cyanamide Co. (*Brit. Appl.* 14357/43).

The formation of alkali 2-nitroalkanesulphonates by interaction of an α -nitro-olefin and alkali hydrogen sulphite was found to be a general reaction; in the absence of oxygen, sulphurous acid behaved in a similar way, giving the free nitro-sulphonic acid, but in the presence of oxygen sulphamic acid was formed, probably by (a) oxidation of sulphurous to sulphuric acid, (b) formation of hydroxylamine from sulphuric acid and the nitro-olefin, and (c) interaction of hydroxylamine and sulphur dioxide. The use of sodium sulphite in this reaction resulted in the formation of the sodium salt of the sodium *aci*-nitroalkanesulphonate, and in two cases esters of 2-nitro-alcohols have been shown to react in the same way as the nitro-olefins.

Accurate analyses of the nitroalkanesulphonates were not easy to obtain owing to the difficulty of freeing them from the last traces of moisture, and many were characterised as their *p*-toluidine salts (see Chambers and Watt, *J. Org. Chem.*, 1941, 6, 376). All attempts to characterise them by salts of *S*-benzylisothiurea were unsuccessful.

The *sulphonates* which have been prepared are listed in the Table.

Nitro-compound.	Sulphite.	Nitro-sulphonate.
Nitroethylene	NaHSO ₃	Na 2-nitroethanesulphonate
2-Nitroethyl nitrate	NaHSO ₃	Na 2-nitroethanesulphonate
1-Nitroprop-1-ene	NaHSO ₃	Na 1-nitropropane-2-sulphonate
1-Nitroprop-1-ene	H ₂ SO ₃	1-Nitropropane-2-sulphonic acid
1-Nitroprop-1-ene	Na ₂ SO ₃	Na ₂ 1- <i>aci</i> -nitropropane-2-sulphonate
2-Nitroprop-1-ene	NaHSO ₃	Na 2-nitropropane-1-sulphonate
2-Nitropropyl acetate	NaHSO ₃	Na 2-nitropropane-1-sulphonate
1-Nitro-2-methylprop-1-ene	NaHSO ₃	Na 1-nitro-2-methylpropane-2-sulphonate
1-Nitro-2-methylprop-1-ene	H ₂ SO ₃	1-Nitro-2-methylpropane-2-sulphonic acid
2-Nitrobut-2-ene	NaHSO ₃	Na 2-nitrobutane-3-sulphonate and (?) Na 2-oximinobutane-3-sulphonate
2-Nitrostyrene	NaHSO ₃	Na 1-nitro-2-phenylethane-2-sulphonate
2-Nitrostyrene	H ₂ SO ₃	1-Nitro-2-phenylethane-2-sulphonic acid
1-Nitro-2-(2-furyl)ethylene	NaHSO ₃	Na 1-nitro-2-(2-furyl)ethane-2-sulphonate
Ethyl α -nitro- $\beta\beta$ -dimethylacrylate	NaHSO ₃	Na 1-nitro-1-carbethoxy-2-methylpropane-2-sulphonate

A few deviations from the normal reaction course were noted. 1-Nitrocyclohexane and 2-nitro-1-phenylprop-1-ene with sodium hydrogen sulphite gave viscous syrups which could not be characterised and on reduction gave nitrogen-free products. 2-Nitrobut-2-ene, condensed with sodium hydrogen sulphite in an atmosphere of nitrogen, gave a syrupy and a crystalline condensation product both of which on reduction yielded amino-sulphonic acids which, whilst agreeing in analysis with the expected 2-aminobutanesulphonic acid, were not identical. The original crystalline product may be the oximinobutanesulphonic acid, but the structures of the amino-sulphonic acids have not been determined.

The interaction of ethyl α -nitro- $\beta\beta$ -dimethylacrylate and sodium hydrogen sulphite was described by Bouveault and Wahl (*Bull. Soc. chim.*, 1901, 25, 910) who made no attempt to isolate or characterise the reaction product. This has been repeated and the product shown to be that of normal addition.

Reduction of the nitro-sulphonates with Raney nickel and hydrogen gave good yields of the corresponding amino-sulphonic acids; in most cases the reduction was sufficiently facile to

proceed at ordinary temperature and pressure and in only a few was it necessary to use hydrogen under pressure.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

Sodium 2-Nitroethanesulphonate.—(a) *From nitroethylene.* Nitroethylene (27.5 g.; this series, Part I) was added dropwise to a vigorously stirred solution of sodium hydrogen sulphite (39.2 g.) in water (70 c.c.) at -5° to 0° and stirring continued at this temperature for 2 hours and finally at 20° for 4 hours. The mixture was evaporated under reduced pressure at 40° and the residue extracted with absolute alcohol, giving sodium 2-nitroethanesulphonate in 75% yield. The salt was recrystallised from alcohol (Found: N, 7.9. $\text{C}_2\text{H}_4\text{O}_2\text{NSNa}$ requires N, 7.9%). The *p*-toluidine salt, prepared by addition of aqueous *p*-toluidine hydrochloride to the aqueous sodium salt, formed needles from absolute alcohol, m. p. 179° (decomp.) (Found: C, 40.6; H, 5.5; N, 10.6. $\text{C}_9\text{H}_{10}\text{O}_2\text{NS}_2\text{C}_6\text{H}_4\text{N}$ requires C, 41.2; H, 5.4; N, 10.7%).

(b) *From 2-nitroethyl nitrate.* 2-Nitroethyl nitrate (13.6 g.; Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) was added dropwise to a well-stirred solution of sodium hydrogen sulphite (20.8 g.) in water (40 c.c.) at -5° to 0° and stirring was continued for 24 hours at 20° . 2-Nitroethyl nitrate (3.2 g.) was recovered from the solution by ether extraction, and the aqueous layer, after evaporation and extraction as described in (a) above, gave the nitro-sulphonic acid, characterised as its *p*-toluidine salt, in 50% yield.

2-Aminoethanesulphonic Acid.—The nitro-sulphonic acid (above) (1.77 g.) in water (30 c.c.) was shaken with hydrogen and Raney nickel at ordinary temperature and pressure. The filtered solution was evaporated to dryness, treated with concentrated hydrochloric acid, filtered, and again evaporated. The residue on crystallisation from aqueous alcohol afforded 2-aminoethanesulphonic acid (taurine), m. p. 317° (decomp.), in 65% yield. Cortese (*J. Amer. Chem. Soc.*, 1936, 58, 191) gives m. p. $300-305^{\circ}$ (decomp.) (Found: C, 19.2; H, 5.6; N, 10.9. Calc. for $\text{C}_2\text{H}_5\text{O}_2\text{NS}$: C, 19.2; H, 5.6; N, 11.2%).

Sodium 1-Nitropropane-2-sulphonate.—(a) *From sodium hydrogen sulphite.* The salt was prepared from 1-nitroprop-1-ene (17.4 g.; this series, Part I) and sodium hydrogen sulphite (20.8 g.) in water (50 c.c.) as described above for sodium 2-nitroethane sulphonate. Sodium 1-nitropropane-2-sulphonate monohydrate separated from alcohol in 78% yield (Found: C, 17.4; H, 4.1; N, 7.0. $\text{C}_3\text{H}_7\text{O}_2\text{NSNa}\cdot\text{H}_2\text{O}$ requires C, 17.2; H, 3.8; N, 6.7%). The *p*-toluidine salt had m. p. $164-166^{\circ}$ (Found: C, 43.8; H, 5.8; N, 10.2. $\text{C}_8\text{H}_9\text{O}_2\text{NS}_2\text{C}_6\text{H}_4\text{N}$ requires C, 43.5; H, 5.8; N, 10.2%).

(b) *From sulphurous acid.* 1-Nitroprop-1-ene (10 g.) was shaken in a stoppered bottle at room temperature for 2 days with an aqueous solution of sulphurous acid (saturated at 0°). The solution was neutralised with sodium carbonate, evaporated to dryness at 40° under reduced pressure, and the residue extracted with hot absolute alcohol to give sodium 1-nitropropane-2-sulphonate, characterised as the *p*-toluidine salt, m. p. $164-166^{\circ}$.

(c) *From sodium sulphite.* 1-Nitroprop-1-ene (8.7 g.) was gradually added to a vigorously-stirred solution of sodium sulphite heptahydrate (25.2 g.) in water (25 c.c.) at $0-5^{\circ}$ and stirring continued for a further 3 hours at $0-5^{\circ}$ and at 20° for 16 hours. The solution was evaporated to dryness and the residue extracted with absolute alcohol to give disodium 1-aci-nitropropane-2-sulphonate trihydrate, which separated from aqueous alcohol in white crystals (Found: C, 13.6; H, 4.0; N, 5.3. $\text{C}_3\text{H}_6\text{O}_2\text{NSNa}_2\cdot 3\text{H}_2\text{O}$ requires C, 13.6; H, 4.1; N, 5.2%). It was characterised as its *p*-toluidine salt, m. p. $164-166^{\circ}$ alone and in admixture with the sample prepared under (a) above.

1-Aminopropane-2-sulphonic Acid.—The nitro-sulphonic acid (above) was reduced with hydrogen and Raney nickel as described for 2-aminoethanesulphonic acid. The amino-acid, obtained in 79% yield, had m. p. $290-295^{\circ}$ (decomp.) (Gabriel and Colman, *Ber.*, 1906, 39, 2891, give m. p. $290-295^{\circ}$) (Found: C, 25.7; H, 6.5; N, 10.6. Calc. for $\text{C}_3\text{H}_7\text{O}_2\text{NS}$: C, 25.9; H, 6.5; N, 10.1%).

Sodium 2-Nitropropane-1-sulphonate.—(a) *From 2-nitroprop-1-ene.* This was prepared from 2-nitroprop-1-ene (this series, Part I) and sodium hydrogen sulphite as described for sodium 1-nitropropane-2-sulphonate. The salt was crystallised from absolute alcohol, giving sodium 2-nitropropane-1-sulphonate in 88% yield (Found: C, 18.7; H, 4.1; N, 7.0. $\text{C}_3\text{H}_7\text{O}_2\text{NSNa}$ requires C, 18.8; H, 3.1; N, 7.8%).

Catalytic reduction of the salt in the usual way afforded a 60% yield of 2-aminopropane-1-sulphonic acid, which separated from aqueous alcohol, m. p. $325-335^{\circ}$ (decomp.); Gabriel and Ohle (*Ber.*, 1906, 39, 2891) give m. p. 323° (decomp.) (Found: C, 25.9; H, 6.7; N, 10.0. Calc. for $\text{C}_3\text{H}_7\text{O}_2\text{NS}$: C, 25.9; H, 6.5; N, 10.1%).

(b) *From 2-nitropropyl acetate.* A mixture of 2-nitropropyl acetate (7.35 g.; Blomquist, Tapp, and Johnson, *J. Amer. Chem. Soc.*, 1945, 67, 1519), sodium hydrogen sulphite (20.8 g.), and water (50 c.c.) was stirred vigorously at 35° for 16 hours. The homogeneous solution was evaporated to dryness and extracted with absolute alcohol. Evaporation of the alcohol gave a mixture of sodium acetate and sodium 2-nitropropane-1-sulphonate, which was reduced with hydrogen and nickel in the usual way, giving 2-aminopropane-1-sulphonic acid, m. p. $325-328^{\circ}$ (decomp.).

Sodium 1-Nitro-2-methylpropane-2-sulphonate.—(a) *Using sodium hydrogen sulphite.* This reaction was carried out in the normal way using 1-nitro-2-methylprop-1-ene (Levy and Scaife, in the press) in place of the nitropropenes as described above. Recrystallisation from alcohol gave sodium 1-nitro-2-methylpropane-2-sulphonate monohydrate in 95% yield (Found: C, 22.3; H, 4.2; N, 6.1. $\text{C}_4\text{H}_9\text{O}_2\text{NSNa}\cdot\text{H}_2\text{O}$ requires C, 21.5; H, 4.5; N, 6.3%).

(b) *Using sulphurous acid.* The nitro-olefin (10.1 g.) was shaken for 5 days at room temperature in a stoppered bottle with aqueous sulphurous acid (100 c.c. saturated at 0°) in an atmosphere of nitrogen. The solution was neutralised with sodium carbonate and worked up in the normal manner, giving sodium 1-nitro-2-methylpropane-2-sulphonate in 55% yield. In a parallel experiment in which the sulphurous acid solution had been prepared in the presence of air, the only isolated product was sulphamic acid, m. p. 212° (decomp.), obtained in 31% yield, identical with an authentic specimen (Found: H, 3.0; N, 14.3; S, 32.6. Calc. for $\text{H}_2\text{O}_2\text{NS}$: H, 3.1; N, 14.4; S, 33.0%).

1-Amino-2-methylpropane-2-sulphonic Acid.—The nitrosulphonic acid (above) (5 g.) in water (50 c.c.) was reduced with hydrogen and Raney nickel, and the product isolated as described for 2-aminoethanesulphonic acid. **2-Amino-2-methylpropane-2-sulphonic acid** separated from aqueous alcohol as colourless crystals, m. p. 350—360° (decomp.), in 75% yield (Found: C, 31.0; H, 7.2; N, 8.8. $C_4H_9O_2NS$ requires C, 31.3; H, 7.2; N, 9.1%).

Sodium 2-Nitrobutane-3-sulphonate.—2-Nitrobut-2-ene (50.5 g.; this series, Part III) was added dropwise to a cooled solution of sodium hydrogen sulphite (52 g.) in water (120 c.c.). The reaction was carried out in an atmosphere of nitrogen, and stirring was continued for 16 hours. Unreacted 2-nitrobut-2-ene was removed by extraction with ether, the aqueous solution evaporated to dryness under reduced pressure, and the residue extracted with absolute alcohol from which, by evaporation, a pale yellow viscous syrup (80 g.) was obtained. A crystalline solid (10 g.) (see below) separated from this syrup on standing. The syrup, apparently crude sodium 2-nitrobutane-3-sulphonate, gave a *p*-toluidine salt which decomposed below its melting point (Found: C, 45.5; H, 5.8; N, 9.1. $C_8H_{11}O_2NS.C_7H_7N$ requires C, 45.5; H, 6.2; N, 9.6%). Reduction of the syrup with Raney nickel and hydrogen, followed by isolation in the usual way, gave 2-aminobutane-3-sulphonic acid, m. p. 267—270°, in 60% yield (Found: C, 31.3; H, 6.9; N, 9.5. $C_4H_9O_2NS$ requires C, 31.4; H, 7.2; N, 9.2%). The crystalline solid (above) could not be identified with certainty. It may be sodium 2-oximinobutane-3-sulphonate (Found: C, 24.7; H, 4.4; N, 7.4. Calc. for $C_4H_9O_2NSNa$: C, 25.4; H, 4.2; N, 7.4%). The *p*-toluidine salt had m. p. 186—188° (Found: C, 47.1; H, 6.6; N, 10.4. Calc. for $C_8H_{11}O_2NS.C_7H_7N$: C, 48.1; H, 6.6; N, 10.2%). On reduction with hydrogen and Raney nickel in the usual way it gave an amino-acid, m. p. 320—324° (decomp.), in 60% yield (Found: C, 30.6; H, 6.8; N, 9.0. Calc. for $C_4H_9O_2NS$: C, 31.4; H, 7.2; N, 9.2%).

2-Nitro-4-methylpent-2-ene.—To a cooled mixture of isobutaldehyde (36 g.) and diethylamine (10 g.), nitroethane (37.5 g.) was added during 30 minutes, the temperature being kept at 20—30° by intermittent cooling. The mixture was kept at 20° for 15 hours, acidified (2*N*-hydrochloric acid), extracted with ether, and the dried extract fractionated, giving 2-nitro-4-methylpent-2-ene (40.5 g.; 65%, b. p. 67°/10 mm.), as a pale yellow lachrymatory oil (Found: C, 56.2; H, 8.1; N, 10.9. $C_6H_{11}O_2N$ requires C, 55.8; H, 8.5; N, 10.8%).

2-Amino-4-methylpentane-3-sulphonic Acid.—2-Nitro-4-methylpent-2-ene (12.9 g.) in methyl alcohol (35 c.c.) was added dropwise with stirring to a solution of sodium hydrogen sulphite (24 g.) in water (100 c.c.) and methyl alcohol (35 c.c.) at 20°. The mixture was maintained at 30° for 16 hours, evaporated, and extracted with hot absolute alcohol. Concentration of this extract yielded crude sodium 2-nitro-4-methylpentane-3-sulphonate as a pale yellow viscous syrup (yield, 99%), which could not be crystallised. Reduction in aqueous solution with Raney nickel and hydrogen at 25° and 100 atms. (initial pressure) gave 2-amino-4-methylpentane-3-sulphonic acid, white crystals from aqueous alcohol, decomp. > 340°, in 75% yield (Found: C, 40.0; H, 8.3; N, 7.7. $C_6H_{11}O_2NS$ requires C, 39.7; H, 8.3; N, 7.7%).

Sodium 1-Nitro-2-phenylethane-2-sulphonate and 1-Amino-2-phenylethane-2-sulphonic Acid.—(a) *From sodium hydrogen sulphite.* A solution of 2-nitrostyrene (14.9 g.) in dioxan (60 c.c.) was added slowly to a well-stirred solution of sodium hydrogen sulphite (15 g.) in water (90 c.c.) at 20°, and stirring then continued at 30° for 10 hours. Unchanged nitrostyrene was removed with ether, and the aqueous dioxan solution evaporated to dryness. The residue was crystallised from hot absolute alcohol, giving sodium 1-nitro-2-phenylethane-2-sulphonate as white crystals, unmolten at 300°, in 80% yield (Found: N, 5.2. $C_8H_9O_2NSNa$ requires N, 5.5%). Reduction in aqueous solution with Raney nickel and hydrogen at ordinary temperature and pressure, followed by working up in the normal way, afforded 1-amino-2-phenylethane-2-sulphonic acid in 70% yield, pearly plates from aqueous alcohol, m. p. 358—360° (decomp.) (Found: C, 47.1; H, 5.3; N, 7.0. $C_8H_9O_2NS$ requires C, 47.7; H, 5.5; N, 7.0%).

(b) *From sulphurous acid.* 2-Nitrostyrene (10 g.) was shaken with saturated aqueous sulphurous acid (100 c.c.) in a stoppered bottle in the absence of oxygen for 6 days at room temperature. The unreacted nitrostyrene (2.0 g.) was removed by filtration and the solution neutralised with solid sodium carbonate. The crude nitro-acid was reduced with Raney nickel and hydrogen, giving the amino-acid, m. p. 358—360° (decomp.), in 56% yield.

Sodium 1-Nitro-2-(2-furyl)ethane-2-sulphonate.—1-Nitro-2-(2-furyl)ethylene (13.9 g.; Thiele and Landers, *Annalen*, 1909, **369**, 303) in dioxan (50 c.c.) was slowly added to a stirred solution of sodium hydrogen sulphite (24 g.) in water (100 c.c.) and dioxan (50 c.c.) at 25°, and stirring continued for a further 16 hours. The solution was evaporated to dryness, and the residue, extracted with absolute alcohol, gave sodium 1-nitro-2-(2-furyl)ethanesulphonate as a colourless syrup which crystallised slowly on keeping, but could not be recrystallised (Found: C, 26.2; H, 4.2; N, 5.4. $C_8H_9O_2NSNa.2H_2O$ requires C, 25.8; H, 3.6; N, 5.0%). Reduction with Raney nickel and hydrogen in methyl alcohol at ordinary temperature and pressure gave 1-amino-2-(2-furyl)ethane-2-sulphonic acid, white crystals from aqueous dioxan, m. p. 250—252° (decomp.), in 30% yield (Found: N, 7.0. $C_8H_9O_2NS$ requires N, 7.3%).

1-Amino-1-carbethoxy-2-methylpropane-2-sulphonic Acid.—Ethyl α -nitro- $\beta\beta$ -dimethylacrylate (5 g.; Bouveault and Wahl, *Compt. rend.*, 1900, **131**, 687, 748) was added dropwise to a vigorously stirred solution of sodium hydrogen sulphite (5 g.) in water (20 c.c.) at 30°, and stirring was continued for a further 20 hours. The solution was evaporated under reduced pressure and extracted with hot absolute alcohol to give crude sodium 1-nitro-1-carbethoxy-2-methylpropane-2-sulphonate as a colourless glass in 84% yield. Reduction of the above salt (6.7 g.) in water (60 c.c.) with Raney nickel and hydrogen at ordinary temperature and 90 atms. (initial pressure), followed by evaporation of the filtered solution, afforded sodium 1-amino-1-carbethoxy-2-methylpropanesulphonate, white crystals from aqueous alcohol, in 45% yield (Found: N, 5.4. $C_5H_9O_2NSNa$ requires N, 5.7%). Acidification of an aqueous solution of the sodium salt with concentrated hydrochloric acid gave the free amino-sulphonic acid, white crystals from aqueous alcohol, m. p. 223°, in 34% yield (Found: N, 6.0. $C_5H_9O_2NS$ requires N, 6.2%).

Sodium 1-Nitro-2:4:4-trimethylpentane-2-sulphonate.—A mixture of 1-nitro-2:4:4-trimethylpent-1-ene (5 g.; see Levy, Scaife, and Baldock, in the press), dioxan (15 c.c.), and saturated aqueous sodium hydrogen sulphite (50 c.c.) was stirred at 20° for 8 hours. After concentration under reduced

pressure at 20°, the residual white solid was extracted with alcohol, filtered, and the extract treated with dry ether. A white crystalline salt was precipitated, and purified by reprecipitation from alcohol with ether. Sodium 1-nitro-2:4:4-trimethylpentane-2-sulphonate was obtained as white crystals, m. p. 189° (decomp.) (Found: N, 5.4; S, 12.8. $C_8H_{16}O_8NSNa$ requires N, 5.4; S, 12.3%).

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[Received, January 23rd, 1947.]

285. Aliphatic Nitro-compounds. Part VI. Reaction of α -Nitro-olefins with Hydrochloric Acid.

By ROYDEN L. HEATH and J. D. ROSE.

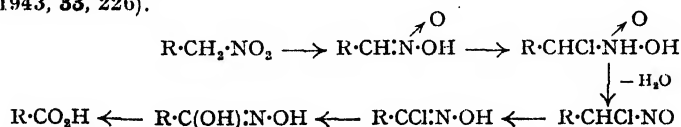
α -Nitro-olefins react with anhydrous hydrogen chloride in ether giving 1:2-dichloronitroso-compounds which rearrange, if an α -hydrogen atom is present, into 1:2-dichloro-oximes. These on hydrolysis with water afford hydroxylamine hydrochloride and an α -hydroxy- or α -chloro-carboxylic acid according to the extent of the hydrolysis. Reaction of the nitro-olefins containing an α -hydrogen atom with concentrated aqueous hydrochloric acid gives similar products, but the intermediate dichloro-oximes are not isolated. It is suggested that the initial step is a 1:4-addition of hydrogen chloride to the nitro-olefin.

THE literature on the action of hydrochloric acid on α -nitro-olefins is scanty. Haitinger (*Monatsh.*, 1881, 2, 287; *Wien Akad. Ber.*, 1878, 77, 428; *A.*, 1879, 700) reported that 1-nitro-2-methylprop-1-ene, treated with hydrogen chloride at 20° or with boiling concentrated hydrochloric acid, gave hydroxylamine hydrochloride, carbon dioxide, and ammonia; a hydroxy-acid, m. p. 65°, was also isolated but not characterised. Our experience, below, suggests that this was probably impure α -hydroxyisobutyric acid (m. p. 79—80°). Priebis (*Annalen*, 1884, 225, 319) obtained phenylchloroacetic acid by treatment of β -nitrostyrene with fuming hydrochloric acid at 100°.

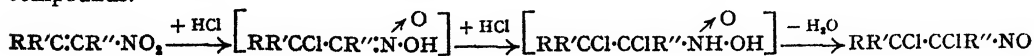
A study of the action of hydrochloric acid on α -nitro-olefins was undertaken as part of a general exploration of the chemistry of the aliphatic nitro-compounds. In the case of nitro-olefins with an α -hydrogen atom ($R_2C:CH:NO_2$), treatment with ethereal hydrogen chloride gave hydroxylamine hydrochloride and an α -chloro- or α -hydroxy-acid (cf. Priebis, *loc. cit.*).

The possibility that the first stage in the reaction was 1:2-addition of hydrogen chloride to the double bond was excluded when it was found that 2-nitroisopropyl chloride, $Me\cdot CHCl\cdot CH_2\cdot NO_2$, was not affected by ethereal hydrogen chloride under the conditions which converted 1-nitroprop-1-ene, $Me\cdot CH_2\cdot CH:NO_2$, into α -chloropropionic acid and hydroxylamine

hydrochloride. It therefore follows that the first addition is 1:4- to give $R_2CCl:CH:N\cdot OH$, which, as the *aci*-form of a primary nitro-paraffin, breaks down *via* the hydroxamic acid to hydroxylamine hydrochloride and an α -chloro- or α -hydroxy-acid (depending on the lability of the chlorine atom). The mechanism of conversion of the *aci*-primary nitro-paraffin into hydroxamic acid is still obscure but is considered to involve the following steps (cf. Yale, *Chem. Reviews*, 1943, 33, 226).



In this mechanism, an important stage is the rearrangement of the 1-chloronitroso-compound to an oxime, which requires a hydrogen atom on the carbon carrying the nitroso-group. From secondary nitro-paraffins, in which this hydrogen is not available, the product expected would therefore be a 1-chloronitroso-compound or its breakdown products. In agreement with this we have found that treatment of nitro-olefins of the type $RR'C:CR''\cdot NO_2$ with ethereal hydrochloric acid gives deep blue highly lachrymatory liquids. Although it has not been possible to obtain these analytically pure on account of the closeness of their boiling points to those of the parent nitro-olefins, there seems little doubt that these are the dichloronitroso-compounds.



Attempts to break down these dichloronitroso-compounds by further treatment with hydrochloric acid gave a trace of hydroxylamine hydrochloride as the only product identified.

EXPERIMENTAL.

Action of Anhydrous Hydrogen Chloride on Nitroethylene.—Nitroethylene (37 g.; this series, Part I) was added dropwise to stirred saturated ethereal hydrogen chloride (300 c.c.) below 0°. Stirring was continued at 0° for 4 hours and at 20° for a further 12 hours. After removal of the ether under reduced pressure $\alpha\beta$ -dichloroacetaldoxime remained as a colourless mobile liquid which began to decompose immediately. The crude product was stirred with water (300 c.c.) at 20° for 16 hours; the mixture, which was homogeneous, still gave a positive test for a hydroxamic acid and was refluxed for $\frac{1}{2}$ hour (hydroxamic acid test negative) and evaporated to dryness under reduced pressure. The residue was extracted with ether, giving chloroacetic acid (39 g.; 82%), m. p. 62–63°, after recrystallisation from chloroform, and hydroxylamine hydrochloride (31.5 g.; 90%) as the ether-insoluble product.

Action of Concentrated Hydrochloric Acid on 2-Nitroethyl Alcohol.—2-Nitroethyl alcohol (10 g.; Levy, Scaife, and Wilder-Smith, J., 1946, 1096) was heated at 140° for 12 hours with concentrated hydrochloric acid (80 c.c.) in a sealed tube. The solution was evaporated and separated by ether into chloroacetic acid (6.2 g.; 60%) and hydroxylamine hydrochloride (5.3 g.; 70%).

Action of Anhydrous Hydrogen Chloride on 1-Nitroprop-1-ene.—This was carried out using 1-nitroprop-1-ene (51 g.; this series, Part I) and ethereal hydrogen chloride (250 c.c.) as described above for nitroethylene. The $\alpha\beta$ -dichloropropaldoxime was distilled (80%), b. p. 78–80°/12 mm., but began to decompose immediately after distillation. A portion (37 g.) was hydrolysed by refluxing it with water (100 c.c.) for $\frac{1}{2}$ hour. After evaporation the residue was separated by ether into lactic acid (8.0 g.; 33%), α -chloropropionic acid (0.7 g.; 2%), and hydroxylamine hydrochloride (10.4 g.; 60%).

Action of Concentrated Hydrochloric Acid on 1-Nitroprop-1-ene and 2-Nitroisopropyl Alcohol.—1-Nitroprop-1-ene (20 g.) was stirred with concentrated hydrochloric acid (100 c.c.) at 20° for 24 hours and then at 40° for 2 hours. After working up in the usual way, hydroxylamine hydrochloride (12 g.; 75%), lactic acid (6.0 g.; 30%), and α -chloropropionic acid (0.5 g.; 2%) were obtained. Similarly, 2-nitroisopropyl alcohol (10.5 g.) heated at 140° for 2 hours with concentrated hydrochloric acid (sealed tube) gave hydroxylamine hydrochloride (5.3 g.; 75%) and α -chloropropionic acid (5.6 g.; 54%).

Action of Anhydrous Hydrogen Chloride on 2-Nitroprop-1-ene.—2-Nitroprop-1-ene (26.1 g.; this series, Part I) was added dropwise with stirring to dry ether saturated at 0° with anhydrous hydrogen chloride (200 c.c.); a deep blue colour rapidly developed. Stirring was continued at 0° and precipitated hydroxylamine hydrochloride (1.8 g.) removed. Separated water was absorbed by the addition of anhydrous magnesium sulphate, and the solution distilled giving 1:2-dichloro-2-nitrosopropane, b. p. 48–50°/60 mm., as a deep blue, mobile, powerfully lachrymatory liquid (20 g.; 45%). It was not possible to obtain this material analytically pure owing to difficulties of separating small amounts of unchanged 2-nitroprop-1-ene (b. p. 45–48°/60 mm.).

Action of Anhydrous Hydrogen Chloride on 2-Nitrobut-2-ene.—2-Nitrobut-2-ene (20.2 g.; this series, Part III) was treated as described above for 2-nitroprop-1-ene. 2:3-Dichloro-2-nitrosobutane, b. p. 61–63°/40 mm., was obtained as a deep blue lachrymatory liquid (11 g.; 35%). After hydrolysis with water at 20° for 16 hours only hydroxylamine hydrochloride (0.1 g.) could be identified.

Action of Concentrated Hydrochloric Acid on 2-Nitrobut-2-ene.—2-Nitrobut-2-ene (20 g.) was stirred at 20° for 40 hours with concentrated hydrochloric acid (100 c.c.). The deep blue colour which developed initially disappeared in $\frac{1}{2}$ hour. Evaporation to dryness under reduced pressure gave only hydroxylamine hydrochloride (7 g.; 52%).

Action of Anhydrous Hydrogen Chloride on 1-Nitro-2-methylprop-1-ene.—1-Nitro-2-methylprop-1-ene (60 g.; Levy and Scaife, in the press) was treated with saturated ethereal hydrogen chloride (400 c.c.) as described above for nitroethylene. $\alpha\beta$ -Dichloroisobutaldoxime, b. p. 79°/10 mm., was obtained as a colourless liquid which began to decompose immediately after distillation (75 g.; 80%). Hydrolysis of this dichloro-oxime (24 g.) with boiling water (250 c.c.) for 16 hours gave hydroxylamine hydrochloride (9.5 g.; 90%) and α -hydroxyisobutyric acid, m. p. 80° (4.8 g.; 30%). Hydrolysis of the dichloro-oxime with concentrated hydrochloric acid for $1\frac{1}{2}$ hours gave a 50% yield of α -hydroxyisobutyric acid.

Action of Concentrated Hydrochloric Acid on 1-Nitro-2-methylprop-1-ene.—1-Nitro-2-methylprop-1-ene (20.2 g.) was added dropwise with vigorous stirring to concentrated hydrochloric acid (100 c.c.) at 15–20°. Stirring was continued for 16 hours, and the mixture then boiled for 15 minutes and worked up in the usual way, giving hydroxylamine hydrochloride (12 g.; 86%) and α -hydroxyisobutyric acid (11.3 g.; 54%).

Action of Anhydrous Hydrogen Chloride on 1-Nitro-2-chloropropane.—1-Nitro-2-chloropropane (Henry, Bull. Soc. chim., 1895, 13, 1000) was treated with anhydrous ethereal hydrogen chloride under the conditions described for 1-nitroprop-1-ene (see above). On distillation unchanged 1-nitro-2-chloropropane, b. p. 60–65°/14 mm., was recovered quantitatively.

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[Received, January 23rd, 1947.]

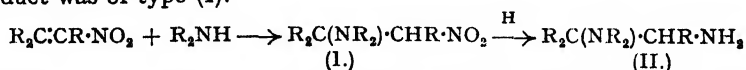
286. Aliphatic Nitro-compounds. Part VII. Preparation of 2-Nitroalkylamines.

By R. L. HEATH and J. D. ROSE.

Ammonia and primary or secondary amines interact with α -nitro-olefins, giving 2-nitroalkylamines. Those formed from ammonia or aliphatic amines are in general extremely unstable, but can be reduced by nickel and hydrogen to derivatives of ethylenediamine. N-2-Nitroalkylarylamines formed from aromatic amines are somewhat more stable, but are best isolated and characterised through their salts. In many cases 2-nitroethyl nitrate can be

used as a convenient laboratory substitute for nitroethylene, and 2-nitroisopropyl acetate or 2-nitroisopropyl nitrate can replace 1-nitroprop-1-ene.

THE addition of ammonia and amines to α -nitro-olefins has hitherto received only scant attention in the literature. The reaction of nitroethylene with aniline (Wieland and Sakellarios, *Ber.*, 1919, 52, 898) and nuclear substituted anilines (Kodak Ltd., B.P. 539,070; 21.2.40) is known to give *N*-2-nitroethylanilines, but in most cases the products were not characterised and experimental details are lacking. β -Nitrostyrene reacts with hydroxylamine to give $\text{Ph}\cdot\text{CH}(\text{NH}\cdot\text{OH})\cdot\text{CH}_2\cdot\text{NO}_2$ (Posner, *Annalen*, 1912, 389, 114), but the reaction with other bases is erratic. Worrall (*J. Amer. Chem. Soc.*, 1927, 49, 1598) attempted to add some forty bases (amines, hydrazines) to β -nitrostyrene and found that only thirteen gave isolatable adducts. Aniline and *p*-toluidine were the only common aromatic bases and piperidine the only secondary amine with which he was able to obtain an adduct, and in each of these three cases the adduct was of type (I).



The addition of ammonia was, however, exceptional, two mols. of β -nitrostyrene being involved to give $\text{NH}(\text{CHPh}\cdot\text{CH}_2\cdot\text{NO}_2)_2$.

Halogen-substituted nitro-olefins have also been reported to react with amines. Thus β -bromo- β -nitrostyrene with ammonia gives 2-bromo-2-nitro-1-phenylethylamine (Loevenich and Gerber, *Ber.*, 1930, 63, 1707), and 1-bromo-1-nitrobut-1-ene with aliphatic amines gives unstable adducts (Loevenich, Koch, and Pucknat, *Ber.*, 1930, 63, 636).

A study of the addition of amines to nitro-olefins has now been undertaken as part of a general investigation of the aliphatic nitro-compounds and as a possible route to certain substituted derivatives of ethylenediamine required for other work.

The addition of ammonia and amines to nitro-olefins is a general reaction which in most cases proceeds very readily. The yields are variable, but this is due to the instability of the resulting 2-nitroalkylamine in which the basic group causes rapid decomposition of the primary or secondary nitro-compound. The products from aromatic amines are weaker bases than those from ammonia or aliphatic amines and are therefore more stable, but in both series it was found preferable to isolate the adducts as salts. Hydrogenation of the 2-nitroalkylamines to ethylenediamines was carried out using Raney nickel.

A complication in carrying out these additions was the tendency of the nitro-olefins to polymerise under the influence of the amine. It was found that better yields of some adducts were obtained when esters of the corresponding 2-nitro-alcohols were used in place of the nitro-olefin. Thus 2-nitroethyl nitrate and 2-nitroisopropyl acetate could be used to replace nitroethylene and 1-nitroprop-1-ene, respectively.

Ammonia has been caused to react with 2-nitroethyl nitrate, 1-nitroprop-1-ene, 2-nitrobut-2-ene, and 1-nitro-2-methylprop-1-ene to give the corresponding unstable β -nitro-amines (type I) which were characterised as salts. Hydrogenation of the nitro-amines over Raney nickel gave the 1:2-diamines (type II). Similarly, diethylamine reacted with 2-nitroethyl nitrate and 2-nitrobut-2-ene to give nitro-amines (type I). From 1:2:3:4-tetrahydroquinoline, the *N*-2-nitroethyl derivative was obtained in 75% yield from 2-nitroethyl nitrate, but in only 12.5% yield from nitroethylene itself.

Aniline has been caused to react with nitroethylene, 2-nitroethyl nitrate, 1-nitroprop-1-ene, and 2-nitrobut-2-ene; *N*-methylaniline with nitroethylene, 1-nitroprop-1-ene, and 2-nitroisopropyl acetate; *N*-ethylaniline with nitroethylene, 2-nitroethyl nitrate, and 1-nitroprop-1-ene. All the products were of type I and readily reverted to nitro-olefin and amine on treatment with alkali (which polymerised the nitro-olefin formed), and in some cases dilute acid affected the same fission. A bis-adduct, *di*-(2-nitroethyl)aniline, was isolated as its hydrochloride after further reaction of *N*-2-nitroethylaniline with nitroethylene; this salt eliminated nitroethylene on being heated in water. There was evidence that 2-nitroethylaniline reacted with 1-nitroprop-1-ene, but the product was too unstable for isolation.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. M. ps. are uncorrected.

2-Nitroethylamine and Ethylenediamine.—2-Nitroethyl nitrate (13.6 g.; Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) was added dropwise with stirring to methyl alcohol (200 c.c.) saturated with dry ammonia at -5° , and stirring continued for 4 hours at -5° to 0° . The mixture was filtered and the filtrate evaporated at 40° under reduced pressure to give a light brown oil (9 g.). The crude 2-nitro-

ethylamine could not be distilled, did not give a crystalline hydrochloride or picrate, and decomposed to a black tar in 1 to 2 hours. The crude product (8 g.) in methyl alcohol (300 c.c.) was shaken with hydrogen and Raney nickel at ordinary temperature and pressure; the hydrogen absorption was almost theoretical. The mixture was filtered, acidified with hydrochloric acid, and evaporated to dryness; the semi-solid crystalline mass was intimately mixed with powdered potassium hydroxide and dry distilled to give an aqueous solution of ethylenediamine (5.4 g.), b. p. 100–110°; the dipicrate, m. p. 232–234° (decomp.), was identical with an authentic specimen.

2-Nitroisopropylamine.—1-Nitroprop-1-ene (30 g.; this series, Part I) was added with stirring to methyl-alcoholic ammonia (200 c.c.) at 0° and stirring continued for 3 hours. The solution was evaporated and distilled, giving 2-nitroisopropylamine, b. p. 50–55°/10 mm. Yield, 55%. 2-Nitroisopropylamine is very unstable and decomposes in 24 hours. The hydrochloride had m. p. 114° (Found: C, 26.0; H, 6.4; Cl, 25.5. $C_3H_7O_2N_2.HCl$ requires C, 25.6; H, 6.4; Cl, 25.3%).

1:2-Diaminopropane.—The nitroamine (above) (10 g.) in methyl alcohol (400 c.c.) was shaken with hydrogen in the presence of Raney nickel at ordinary temperature and pressure. The theoretical amount of hydrogen was absorbed. The solution was filtered, acidified with concentrated hydrochloric acid, and evaporated to dryness at 40° under reduced pressure to give 1:2-diaminopropane dihydrochloride which crystallised in long needles from alcohol-ether, m. p. 221° (Strache, *Ber.*, 1888, 21, 2359, gives m. p. 220°). Yield, 52%. The dipicrate formed yellow needles from water, m. p. 237° (Windaus, Dorries, and Jensen, *Ber.*, 1921, 54, 2750, give m. p. 237°).

Di-(2-nitroisopropyl)amine.—Dry ammonia was passed for 1 hour through a solution of 2-nitroisopropyl nitrate (30 g.; Levy and Scaife, *J.*, 1946, 1100) in dry ether (200 c.c.). The solution, filtered from ammonium nitrate (15.7 g.), was fractionated, giving *di*-(2-nitroisopropyl)amine, b. p. 60–62°/0.5 mm. Yield, 12.7 g. (Found: N, 21.6. $C_6H_{13}O_4N_4$ requires N, 22.0%).

2-Nitro-3-aminobutane.—2-Nitrobut-2-ene (20.2 g.; this series, Part III) was added dropwise with stirring to methyl-alcoholic ammonia (250 c.c.) at 0° and stirring continued for 2 hours. The solution was evaporated and distilled, giving 2-nitro-3-aminobutane as an almost colourless liquid, b. p. 75–78°/20 mm., n_D^{20} 1.4720 (60%), which decomposed in 2 days. The hydrochloride, m. p. 115° (decomp.), was also unstable (Found: Cl, 23.4. $C_4H_{10}O_2N_2.HCl$ requires Cl, 23.0%).

2:3-Diaminobutane.—2-Nitro-3-aminobutane (6 g.) in methyl alcohol (60 c.c.) was shaken with hydrogen in the presence of Raney nickel. When absorption was complete the solution was filtered, acidified with hydrochloric acid, evaporated to dryness, and the crystalline residue of the dihydrochloride recrystallised from aqueous alcohol to m. p. 312°. Yield, 40% (Found: C, 20.8; H, 8.2; N, 17.4. $C_4H_{12}N_2.2HCl$ requires C, 20.8; H, 8.7; N, 17.4%). Angeli (*Ber.*, 1890, 23, 1357) reports that the dihydrochloride of 2:3-diaminobutane is crystalline, but gives no m. p. The picrate decomposed at 250–252° (Morgan and Hickinbottom, *J. Soc. Chem. Ind.*, 1924, 43, 3097, give m. p. 250–252°).

1-Nitro-2-amino-2-methylpropane.—Dry ammonia was passed into a solution of 1-nitro-2-methylprop-1-ene (Levy and Scaife, in the press) in dry benzene (100 c.c.) at 20° for 8 hours, and the solution then distilled giving 1-nitro-2-amino-2-methylpropane as an oil, b. p. 62–65°/11 mm., in 40% yield. The nitroamine was unstable and decomposed in 3–4 days. The hydrochloride, from absolute alcohol, had m. p. 182° (decomp.) (Found: N, 18.1; Cl, 22.9. $C_4H_{10}O_2N_2.HCl$ requires N, 18.1; Cl, 23.0%). Reduction of the nitroamine with Raney nickel and hydrogen afforded 1:2-diamino-2-methylpropane isolated in 75% yield as the dihydrochloride, m. p. 302°. Strack and Schwaneberg (*Ber.*, 1933, 66, 1333) give m. p. 303° (Found: Cl, 44.2. Calc. for $C_4H_{12}N_2.2HCl$: Cl, 44.1%).

Diethyl-2-nitroethylamine.—2-Nitroethyl nitrate (6.8 g.) was added dropwise with stirring to diethylamine (7.3 g.) in dry ether (100 c.c.) kept at 0° by external cooling. After the addition was complete, stirring was continued for $\frac{1}{2}$ hour. The solution was filtered and the ether removed at 20° under reduced pressure. An attempt to distil a small portion of the residue at 15 mm. was unsuccessful; the product decomposed violently. The hydrochloride, from alcohol-ether, had m. p. 72–75° (Found: Cl, 19.3. $C_6H_{14}O_2N_2.HCl$ requires Cl, 19.4%). The picrate formed needles from alcohol, m. p. 88° (Found: C, 38.6; H, 4.8; N, 18.4. $C_8H_{16}O_4N_4$ requires C, 38.2; H, 5.0; N, 18.5%).

2-Nitro-3-diethylaminobutane.—2-Nitrobut-2-ene (10.1 g.) in dry ether (10 c.c.) was added dropwise with stirring to diethylamine (7.3 g.) in dry ether (25 c.c.) at 0–10° and the mixture stirred for a further 2 hours. The product was fractionated to give 2-nitro-3-diethylaminobutane, b. p. 90–95°/11 mm., in 65% yield. Much decomposition had occurred after 12 hours. The picrolonate had m. p. 267° (decomp.) (Found: C, 49.4; H, 5.4. $C_{12}H_{24}O_2N_2$ requires C, 49.3; H, 5.9%).

N-(2-Nitroethyl)-1:2:3:4-tetrahydroquinoline.—(a) From 2-nitroethyl nitrate. 2-Nitroethyl nitrate (5.9 g.) was added dropwise with stirring to tetrahydroquinoline (11.8 g.), the temperature being kept below 30°. After 1 hour's stirring the product was dissolved in ether (50 c.c.) and washed with water. Ethereal hydrogen chloride was added to the dried ethereal solution and the precipitated hydrochloride crystallised from absolute alcohol, m. p. 132°. Yield, 75% (Found: N, 11.4; Cl, 14.3. $C_{11}H_{14}O_2N_2.HCl$ requires N, 11.5; Cl, 14.6%).

(b) From nitroethylene. A mixture of equimolecular amounts of nitroethylene and tetrahydroquinoline stirred at 40° for 1 hour gave the base, isolated as the hydrochloride, m. p. 132°, in 12.5% yield.

2-Nitroethylaniline.—(a) From nitroethylene. The base was prepared according to Wieland and Sakellarios (*Ber.*, 1919, 52, 898). Yield, 80%; m. p. 37°.

(b) From 2-nitroethyl nitrate. To a well-stirred solution of aniline (37.2 g.) in ether (250 c.c.), 2-nitroethyl nitrate (27.2 g.) was added dropwise at room temperature. After being stirred for 2 hours the ethereal solution was washed with water, dried, and concentrated under reduced pressure below 30°. The resulting syrup crystallised on cooling strongly, and separated from ether-light petroleum in golden plates, m. p. 37° (22 g.; 65%). The hydrochloride formed needles from alcohol-ether, m. p. 109° (Found: N, 13.9. $C_8H_{10}O_2N_2.HCl$ requires N, 13.8%). The acetyl derivative formed long needles from aqueous alcohol, m. p. 99° (Found: N, 13.2. $C_{10}H_{12}O_3N_2$ requires N, 13.4%).

Di-(2-nitroethyl)aniline.—Nitroethylene (3.7 g.) was added with stirring to 2-nitroethylaniline (8.3 g.) at 0–10°. After 2 hours the product was dissolved in a mixture of acetone (50 c.c.) and ether (50 c.c.), and ethereal hydrogen chloride added. The precipitated hydrochloride separated from dry alcohol

containing hydrogen chloride as prisms, m. p. 128° (7.8 g.; 50%) (Found: Cl, 12.7. $C_{10}H_{13}O_4N_3.HCl$ requires Cl, 12.9%). The free base, m. p. 64°, was obtained by crystallising the hydrochloride from aqueous alcohol (Found: C, 50.0; H, 5.7; N, 17.0. $C_{10}H_{13}O_4N_3$ requires C, 50.2; H, 5.4; N, 17.5%).

Methyl-2-nitroethylaniline.—Nitroethylene (3.6 g.) was added dropwise with stirring to methylaniline (5.3 g.) at 0–10° and the reaction completed by heating at 40° for 1 hour; the product distilled at 110°/0.2 mm. (yield, 4.5 g.; 50%). The hydrochloride had m. p. 82° (Found: N, 12.4; Cl, 16.5. $C_9H_{11}O_2N_3.HCl$ requires N, 12.9; Cl, 16.4%).

Ethyl-2-nitroethylaniline.—(a) From 2-nitroethyl nitrate. The preparation was carried out from ethylaniline and 2-nitroethyl nitrate as described under (b) above for the preparation of 2-nitroethylaniline. The product was isolated in 80% yield as the hydrochloride, m. p. 114° (Found: N, 12.2; Cl, 15.3. $C_{10}H_{14}O_2N_3.HCl$ requires N, 12.2; Cl, 15.4%). The free base was formed by gradual addition of solid sodium carbonate (6.6 g.) to a fine suspension of the hydrochloride (30 g.) in water (100 c.c.) at 0–5°. Ethyl-2-nitroethylaniline separated as a pale green oil which was isolated by ether and distilled, b. p. 108°/0.1 mm., n_D^{20} 1.5597. Yield, 70% (Found: C, 61.8; H, 7.2; N, 14.4. $C_{10}H_{14}O_2N_3$ requires C, 61.8; H, 7.2; N, 14.4%). The picrate, from alcohol, had m. p. 106° (Found: C, 45.9; H, 4.5; N, 16.3. $C_{10}H_{14}O_2N_3.C_6H_3O_7N_3$ requires C, 45.4; H, 4.0; N, 16.5%).

(b) From nitroethylene. The preparation was carried out as described above for the preparation of methyl-2-nitroethylaniline, and the hydrochloride, m. p. 114°, isolated in 75% yield.

2-Nitroisopropylaniline.—This was prepared from 1-nitroprop-1-ene (8.7 g.) and aniline (9.3 g.) in ether (100 c.c.) at room temperature for 2 hours. Removal of the ether under reduced pressure gave a yellow oil which solidified on cooling to –50°, and was crystallised from alcohol, giving yellow needles of 2-nitroisopropylaniline, m. p. 33° (Found: C, 60.05; H, 6.45; N, 15.2. $C_9H_{11}O_2N_3$ requires C, 60.0; H, 6.6; N, 15.5%). The hydrochloride, from 2N-hydrochloric acid, had m. p. 148° (Found: N, 12.8; Cl, 16.6. Calc. for $C_9H_{11}O_2N_3.HCl$: N, 12.9; Cl, 16.4%). Fourncau (*Bull. Soc. chim.*, 1944, 11, 143) gives m. p. 141°.

Methyl-2-nitroisopropylaniline.—(a) From 1-nitroprop-1-ene. Methylaniline (53.5 g.) was added dropwise to well stirred 1-nitroprop-1-ene (43 g.), the temperature being kept below 30° by external cooling. The crude product was dissolved in ether (500 c.c.) and added slowly with stirring to cool ethereal hydrogen chloride (500 c.c. containing 20 g. of hydrogen chloride). The separated solid was triturated twice with methyl alcohol-ether (1 : 2), giving the pure hydrochloride (106 g.; 92%), m. p. 126° (Found: Cl, 15.5. $C_{10}H_{14}O_2N_3.HCl$ requires Cl, 15.3%). The hydrochloride, which is largely hydrolysed in aqueous solution, was treated in water with sodium carbonate, giving a pale green oil, which was isolated with ether and distilled, yielding methyl-2-nitroisopropylaniline, b. p. 112–115°/0.5 mm., in 80% yield (Found: C, 62.3; H, 7.2. $C_{10}H_{14}O_2N_3$ requires C, 61.8; H, 7.2%). The picrate had m. p. 116° (Found: C, 45.3; H, 4.3; N, 16.8. $C_{10}H_{14}O_2N_3.C_6H_3O_7N_3$ requires C, 45.4; H, 4.0; N, 16.6%). The perchlorate formed colourless prisms from alcohol-ether, m. p. 116° (Found: C, 40.3; H, 5.1; N, 9.4. $C_{10}H_{14}O_2N_3.HClO_4$ requires C, 40.7; H, 5.1; N, 9.5%). The hydrochloride of the p-nitroso-derivative, prepared by nitrosation of the hydrochloride, formed dark green crystals from methyl alcohol, and decomposed at 160° (Found: C, 46.4; H, 5.2. $C_{10}H_{13}O_3N_3.HCl$ requires C, 46.2; H, 5.4%).

(b) From 2-nitroisopropyl acetate. A mixture of methylaniline (5.3 g.) and 2-nitroisopropyl acetate (7.4 g.; Schmidt and Rutz, *Ber.*, 1928, 61, 2142) was heated at 50° for 8 hours. The crude product was converted into the hydrochloride, m. p. 126°, which was obtained in 50% yield.

Ethyl-2-nitroisopropylaniline.—This was prepared from 1-nitroprop-1-ene and ethylaniline as described for methyl-2-nitroethylaniline above. The hydrochloride, from alcohol, had m. p. 123°. Yield, 90% (Found: C, 54.1; H, 6.7; N, 11.3. $C_{11}H_{16}O_2N_3.HCl$ requires C, 53.9; H, 6.9; N, 11.4%).

Ethyl-2-nitro-n-propylaniline.—This was prepared from 2-nitroprop-1-ene (58 g.) and ethylaniline (80 g.) in ether (250 c.c.) as described for the isomeride above. It was isolated as the hydrochloride, m. p. 126°, in 50% yield (Found: C, 54.1; H, 6.9; N, 11.3. $C_{11}H_{16}O_2N_3.HCl$ requires C, 53.9; H, 6.9; N, 11.4%).

2-Nitro-1-methyl-n-propylaniline.—2-Nitrobut-2-ene (24 g.) was added dropwise with stirring to aniline (18.6 g.) at 20°, the mixture maintained at 30° for 3 hours, and distilled, giving the base, b. p. 86°/0.5 mm., n_D^{20} 1.5570, in 72% yield. The hydrochloride, from methyl alcohol-ether, had m. p. 122° (Found: C, 52.4; H, 6.5; N, 12.0. $C_{10}H_{14}O_2N_3.HCl$ requires C, 52.1; H, 6.5; N, 12.1%). The perchlorate explodes on warming (Found: C, 41.1; H, 5.2; N, 9.4. $C_{10}H_{14}O_2N_3.HClO_4$ requires C, 40.7; H, 5.1; N, 9.5%).

The authors wish to acknowledge the advice and encouragement of Mr. C. Paine and Dr. H. A. Piggott.

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[Received, January 23rd, 1947.]

287. Aliphatic Nitro-compounds. Part VIII. Addition of Primary and Secondary Nitro-paraffins to α -Nitro-olefins to give 1 : 3-Dinitro-paraffins.*

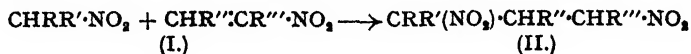
By A. LAMBERT and H. A. PIGGOTT.

Interaction of primary or secondary aliphatic nitro-compounds with α -nitro-olefins yields 1 : 3-dinitro-paraffins, which on reduction afford 1 : 3-diamines. The reaction appears to be a general one, but yields are variable. An attempted condensation of 2 : 4-dinitro-2 : 3-dimethylpentane with formaldehyde gave, surprisingly, methyl 2-nitro-1 : 2-dimethylpropyl ketoxime.

* Patent application pending.

MANY authors have described the addition of nitro-paraffins to activated ethylenic systems, including $\alpha\beta$ -unsaturated ketones (Kohler, *J. Amer. Chem. Soc.*, 1916, **38**, 889, and later papers), unsaturated esters (Kohler and Engelbrecht, *ibid.*, 1919, **41**, 764), and nitriles (Bruns, *ibid.*, 1943, **65**, 23), but little attention has been paid to their addition to the α -nitro-olefins. Worrall (*ibid.*, 1935, **57**, 2299; cf. Heim, *Ber.*, 1911, **44**, 2016) recorded the interaction of α -nitrostilbene and phenylnitromethane in the presence of ammonia to give 1:3-dinitro-1:2:3-triphenylpropane, and since the present work was completed, Hass (*Ind. Eng. Chem.*, 1943, **35**, 1151) has mentioned the formation of 1:3-dinitro-2:3-dimethylpropane from nitromethane and 1-nitro-2-methylpropene, but in neither case was experimental detail presented.

A systematic investigation of the addition of nitro-paraffins to nitro-olefins was undertaken as part of a general exploration of the addition reactions of the nitro-olefins and as a possible route to a wide variety of substituted 1:3-diamines of interest in connection with other work in these laboratories. The addition of a primary or secondary nitro-paraffin to a nitro-olefin, although a general reaction, afforded the 1:3-dinitro-paraffins in extremely variable yields.



Thus, 2-nitrobut-2-ene (I, $\text{R}' = \text{R}'' = \text{CH}_3$) and 2-nitropropane in presence of sodium ethoxide yielded 47% of 2:4-dinitro-2:3-dimethylpentane (II, $\text{R} = \text{R}' = \text{R}'' = \text{R}''' = \text{Me}$); in this case the nitro-olefin is not easily polymerised by alkali, the product, containing only one active hydrogen atom, does not easily interact further with unchanged nitro-olefin, and the amount of polymeric by-product was therefore negligible. In the presence of benzyltrimethylammonium hydroxide, nitroethane and 2-nitrobut-2-ene gave the dissecondary nitro-paraffin, 2:4-dinitro-3-methylpentane, in 28% yield with a considerable amount of by-product of high molecular weight which decomposed on attempted distillation; with sodium ethoxide or piperidine as catalyst the same product was obtained in lower yield. 2-Nitropropane and 2-nitroprop-1-ene gave (sodium ethoxide catalyst) 2:4-dinitro-2-methylpentane in 26% yield, and methyl 2-nitropropyl sulphide and methyl 2-nitropropyl ether (see Parts IV and III in this series) added (sodium methoxide catalyst) to 2-nitroprop-1-ene to give methyl 2:4-dinitro-2-methylamyl sulphide and methyl 2:4-dinitro-2-methylamyl ether, respectively; the latter was also obtained directly in 52% yield from two molecules of 2-nitroprop-1-ene and one of sodium methoxide without isolation of the intermediate methyl 2-nitropropyl ether. The higher nitro-olefins were less reactive; thus, 2-nitropropane and 1-nitrocyclohexene gave nitro-2-(1-nitroisopropyl)-cyclohexane in only 16% yield.

The properties of the 1:3-dinitro-paraffins are parallel to those of the simpler mononitro-compounds; they exhibit none of the instability associated with the 1:2-dinitro-paraffins. Hydrogenation in the presence of nickel catalysts affords 1:3-diamines; they dissolve in aqueous alkali and treatment of such solutions with bromine gives the α -bromo-derivatives which are useful for characterisation purposes. Surprising results were obtained in an attempt to cause 2:4-dinitro-2:3-dimethylpentane to interact with paraformaldehyde and sodium hydroxide; instead of the expected 4-hydroxymethyl derivative, methyl 2-nitro-1:2-dimethylpropyl ketoxime, m. p. 51° , was formed. This is the only known example of the reduction of a secondary nitro-paraffin by formaldehyde and alkali; the structure of the oxime was confirmed by reduction of the sodium salt of the dinitro-compound with stannous chloride and hydrochloric acid, a method specific for the reduction of primary or secondary nitro-paraffins to oximes (cf. Konowalov, *J. Russ. Phys. Chem. Soc.*, 1898, **30**, 960; *Chem. Zentr.*, 1899, I, 597). In addition to the oxime, m. p. 51° , above, the isomeride, m. p. $85-86^\circ$, was also formed, which was rearranged with phosphorus pentachloride to an isomeric amide.

The 2-nitroprop-1-ene used in this work was prepared by the method of Buckley and Scaife (this series, Part I).

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. M. ps. are uncorrected.

2:4-Dinitro-2:3-dimethylpentane.—A well-stirred solution of sodium ethoxide (39.6 g.) in alcohol (400 c.c.) was treated with 2-nitropropane (52.5 g.) at $15-20^\circ$, followed by 2-nitrobut-2-ene (59.5 g.; this series, Part III), and the whole refluxed. After cooling, the mixture was poured into iced water (1000 c.c.) and neutralised at 0° with 2*N*-hydrochloric acid. The solution was concentrated under reduced pressure and the residue extracted with ether. Distillation gave 2:4-dinitro-2:3-dimethylpentane (53 g.) as a pale yellow oil, b. p. $90-92^\circ/0.5$ mm. (Found: C, 44.9; H, 7.5; N, 14.5. $\text{C}_7\text{H}_{14}\text{O}_4\text{N}_2$ requires C, 44.2; H, 7.4; N, 14.7%). The 2-bromo-derivative, prepared from an aqueous solution of sodium 2:4-dinitro-2:3-dimethylpentane and the calculated quantity of bromine, formed colourless plates from methyl alcohol, m. p. 40° (Found: C, 30.8; H, 4.7; N, 10.3; Br, 29.7. $\text{C}_7\text{H}_{13}\text{O}_4\text{N}_2\text{Br}$

requires C, 31.2; H, 4.8; N, 10.4; Br, 29.7%). The 2-(*p*-nitrophenylazo)-derivative, prepared from sodium 2:4-dinitro-2:3-dimethylpentane and diazotised *p*-nitroaniline (cf. Feasley and Degering, *J. Org. Chem.*, 1943, 8, 12), formed orange prisms from alcohol, m. p. 142–143° (Found: C, 46.2; H, 5.1; N, 20.7. $C_{15}H_{11}O_5N_5$ requires C, 46.0; H, 5.0; N, 20.6%).

2:4-Diamino-2:3-dimethylpentane.—2:4-Dinitro-2:3-dimethylpentane (50 g.) in methyl alcohol was hydrogenated at 50–70° and 70 atm. (initial pressure) over Raney nickel. Fractionation of the product gave 2:4-diamino-2:3-dimethylpentane (17 g.) as a colourless liquid, b. p. 66–68°/30 mm., 180°/754 mm. Reduction with iron and hydrochloric acid gave the same diamine in poor yield. The NN'-dibenzoyl derivative formed colourless needles from benzene, m. p. 175° (Found: C, 74.5; H, 7.4; N, 8.2. $C_{21}H_{19}O_2N_4$ requires C, 74.6; H, 7.7; N, 8.3%). The *platinichloride* formed orange prisms from aqueous alcohol (Found: Pt, 36.1. $C_7H_{15}N_4H_3PtCl_6$ requires Pt, 36.1%).

Methyl 2-Nitro-1:2-dimethylpropyl Ketoxime.—(a) *By reduction with formaldehyde*. 2:4-Dinitro-2:3-dimethylpentane (10 g.), paraformaldehyde (1.6 g.), 40% aqueous sodium hydroxide (0.5 c.c.), and methyl alcohol (20 c.c.) were stirred at room temperature for 16 hours. After neutralisation with dilute hydrochloric acid, fractionation gave a colourless oil (8.2 g.), b. p. 90–91°/0.5 mm., which slowly deposited crystalline material. *Methyl 2-nitro-1:2-dimethylpropyl ketoxime* separated from light petroleum (b. p. 60–80°) as colourless plates, m. p. 51° (Found: C, 47.9; H, 8.1; N, 15.9. $C_7H_{11}O_3N_2$ requires C, 48.2; H, 8.0; N, 16.1%). The *p*-nitrophenylurethane formed fibrous needles from benzene–light petroleum (b. p. 60–80°), m. p. 109–110° (after being dried at 80° in a vacuum) (Found: C, 49.7; H, 5.2; N, 16.3. $C_{14}H_{15}O_3N_4$ requires C, 49.7; H, 5.3; N, 16.6%).

(b) *By reduction with stannous chloride*. A solution of 2:4-dinitro-2:3-dimethylpentane (30 g.) in aqueous sodium hydroxide (12.6%; 50 c.c.) was added dropwise with stirring to a solution of stannous chloride (35 g.) in concentrated hydrochloric acid (210 c.c.) at 0°. After being stirred for a further ½ hour at 0°, the solution was neutralised with sodium carbonate and extracted with ether. Distillation of the extract gave a viscous pale yellow oil (7 g.), b. p. 80–90°/0.1 mm., which crystallised on standing, m. p. and mixed m. p. with the oxime described above, 51°. The *p*-nitrophenylurethane had m. p. 109–110° alone or mixed with the specimen described above. The product from a second similar experiment was crystallised without distillation, giving an isomeric *oxime*, small needles from light petroleum (b. p. 60–80°), m. p. 85–86° (Found: C, 48.5; H, 8.1; N, 15.8. $C_7H_{11}O_3N_2$ requires C, 48.2; H, 8.0; N, 16.1%). With phosphorus pentachloride in dry ether the latter gave an isomeric *amide* which separated from benzene–light petroleum (b. p. 60–80°) in colourless needles, m. p. 83° (Found: C, 47.8; H, 8.2; N, 15.7. $C_7H_{11}O_2N_2$ requires C, 48.2; H, 8.0; N, 16.1%).

2:4-Dinitro-3-methylpentane.—2-Nitrobut-2-ene (50 g.) was added during 1 hour with stirring at ordinary temperature to a mixture of nitroethane (150 g.), dioxan (150 c.c.), and aqueous benzyltrimethylammonium hydroxide (40%; 6 c.c.). After being stirred for 48 hours at 40°, the mixture was diluted with water (500 c.c.) and neutralised with dilute hydrochloric acid. Extraction with ether, followed by fractionation, gave 2:4-dinitro-3-methylpentane (25 g.) as a pale yellow liquid, b. p. 94–95°/0.5 mm. (Found: N, 15.9. $C_8H_{13}O_4N_2$ requires N, 16.2%). The use of piperidine or sodium ethoxide as catalyst in this reaction gave a smaller yield of the same product. The 2:4-dibromo-derivative, prepared by the method described above from 2-bromo-2:4-dinitro-2:3-dimethylpentane, formed colourless prisms from aqueous methyl alcohol, m. p. 53–54° (Found: C, 21.7; H, 3.3; N, 8.0. $C_8H_{10}O_4N_2Br_2$ requires C, 21.6; H, 3.0; N, 8.3%).

2:4-Dinitro-2-methylpentane.—2-Nitropropane (21 g.) was added to 2-nitroprop-1-ene (20 g.; this series, Part I) as described above for the reaction of 2-nitropropane with 2-nitrobut-2-ene. 2:4-Dinitro-2-methylpentane (10.6 g.) was obtained as a pale yellow oil, b. p. 80°/0.2 mm. (Found: C, 41.3; H, 6.7. $C_8H_{13}O_4N_2$ requires C, 40.9; H, 6.8%). The 2-bromo-derivative formed colourless leaflets from aqueous methyl alcohol, m. p. 76° (Found: C, 27.7; H, 4.5; Br, 31.3. $C_8H_{11}O_4N_2Br$ requires C, 28.2; H, 4.3; Br, 31.4%).

2:4-Diamino-2-methylpentane.—2:4-Dinitro-2-methylpentane (9 g.) in methyl alcohol (100 c.c.) was hydrogenated at 70° and 75 atm. (initial pressure) over Raney nickel. The product was filtered, acidified with hydrochloric acid, evaporated to dryness, treated with excess of 50% aqueous potassium hydroxide, and extracted with ether. After drying over potassium hydroxide, distillation gave 2:4-diamino-2-methylpentane as a colourless liquid which fumed on exposure to air, b. p. 150–155°/756 mm. (Kohn, *Monatsh.*, 1902, 23, 6, gives b. p. 147–155°). The NN'-dibenzoyl derivative formed colourless prisms from aqueous methyl alcohol, m. p. 152° (Found: N, 8.6. $C_{20}H_{22}O_2N_4$ requires N, 8.6%).

Nitro-2-(1-nitroisopropyl)cyclohexane.—2-Nitropropane (8.9 g.) was brought into reaction with nitrocyclohexene (12.7 g.) (Wiand *et al.*, *Annalen*, 1921, 424, 71) as described above for the addition of 2-nitropropane to 2-nitrobut-2-ene. Fractionation of the product gave a pale yellow oil (3.5 g.), b. p. 95–110°/0.3 mm., which solidified on cooling, and recrystallised from light petroleum (b. p. 60–80°), giving *nitro-2-(1-nitroisopropyl)cyclohexane* in colourless plates, m. p. 103° (Found: C, 49.9; H, 7.3; N, 12.6. $C_9H_{15}O_3N_2$ requires C, 50.0; H, 7.4; N, 13.0%).

Methyl 2:4-Dinitro-2-methylamyl Ether.—(a) *From methyl 2-nitropropyl ether and 2-nitroprop-1-ene*. A well-stirred solution of sodium methoxide (4.1 g.) in methyl alcohol (50 c.c.) was treated with methyl 2-nitropropyl ether (9.1 g.; this series, Part III), followed by 2-nitroprop-1-ene (6.6 g.) at room temperature. After being stirred at 40–50° for ½ hour, the mixture was poured into iced water (100 c.c.) and neutralised with aqueous acetic acid. The alcohol was distilled under reduced pressure and the residue extracted with ether. Distillation of the ethereal solution gave *methyl 2:4-dinitro-2-methylamyl ether* (8.0 g.) as a pale yellow oil, b. p. 92–94°/0.1 mm. (Found: C, 41.2; H, 6.8; N, 13.1. $C_7H_{11}O_5N_2$ requires C, 40.8; H, 6.8; N, 13.6%). The 4-bromo-derivative formed colourless plates from aqueous methyl alcohol, m. p. 64° (Found: C, 29.6; H, 4.8; N, 9.5; Br, 27.9. $C_7H_{13}O_5N_2Br$ requires C, 29.5; H, 4.6; N, 9.8; Br, 28.1%).

(b) *From 2-nitroprop-1-ene and methyl alcohol*. 2-Nitroprop-1-ene (50 g.) was added dropwise with stirring to a solution of sodium methoxide (15.5 g.) in methyl alcohol (200 c.c.) at 0°. After being stirred at room temperature for ½ hour, the mixture was poured into ice-water (500 c.c.), neutralised with aqueous acetic acid, and extracted with ether. Distillation of the ethereal solution gave *methyl*

2: 4-dinitro-2-methylamyl ether (35 g.), b. p. 94–96°/0.2 mm. The 4-bromo-derivative had m. p. 64°, alone or mixed with the specimen described above.

Methyl 2: 4-Diamino-2-methylamyl Ether.—The dinitro-ether (above) (41.6 g.) in methyl alcohol (650 c.c.) was hydrogenated at 60–70° and 87 atm. (initial pressure). Fractionation of the product gave *methyl 2: 4-diamino-2-methylamyl ether* (20 g.) as a colourless liquid, b. p. 77–79°/10 mm. (Found: N, 18.7. $C_7H_{15}ON_4$ requires N, 19.2%). The *bis*-2: 4-dinitrophenylurea derivative (cf. McVeigh and Rose, J., 1945, 621) had m. p. 190° (Found: C, 44.7; H, 4.5; N, 19.8. $C_{21}H_{24}O_{11}N_8$ requires C, 44.6; H, 4.3; N, 19.9%).

Methyl 2: 4-Dinitro-2-methylamyl Sulphide.—Methyl 2-nitropropyl sulphide (19.6 g.; this series, Part IV) was brought into reaction with 2-nitroprop-1-ene (12.7 g.) as described above for the addition of 2-nitroprop-1-ene to methyl 2-nitropropyl ether. *Methyl 2: 4-dinitro-2-methylamyl sulphide* (10 g.) was obtained as a pale yellow oil, b. p. 110–115°/0.05 mm. (Found: N, 12.1; S, 14.3. $C_7H_{14}O_4N_4S$ requires N, 12.6; S, 14.4%).

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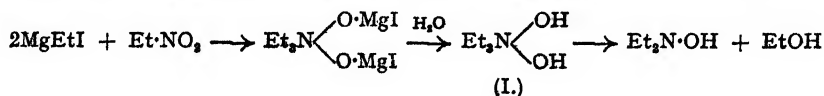
[Received, January 23rd, 1947.]

288. Aliphatic Nitro-compounds. Part IX. Reaction of Nitro-paraffins with Ethylmagnesium Bromide.

By G. D. BUCKLEY.

In the reaction of nitroethane with ethylmagnesium bromide the first stage is addition of the Grignard reagent to the $N=O$ bond to form a complex (III) which on reduction with zinc and hydrochloric acid gives diethylamine. The complex may react with a second mol. of ethylmagnesium bromide with evolution of 1 mol. of ethane to form a new complex which yields *NN*-diethylhydroxylamine on hydrolysis. Nitromethane, 2-nitropropane, and 2-nitro-2-methylpropane form analogous complexes.

THE action of Grignard reagents on nitro-paraffins was first examined by Moureu (*Compt. rend.*, 1901, 132, 837), who observed that nitroethane reacted with 2 mols. of ethylmagnesium iodide to form *NN*-diethylhydroxylamine. He suggested that the reaction involved the direct addition of both mols. of Grignard reagent to the $N=O$ bonds, followed by breakdown on hydrolysis:



Bevad (*Ber.*, 1907, 40, 3065) studied the reactions of primary and secondary nitro-paraffins with several alkyl-zinc and -magnesium iodides. He found that nitroethane reacted with ethylmagnesium iodide with evolution of ethane and a little ethylene to give a complex which on hydrolysis gave *NN*-diethylhydroxylamine accompanied by smaller amounts of diethylamine and ethyl-*sec*-butylhydroxylamine. Ethylzinc iodide reacted in a similar manner, but gave ethyl-*sec*-butylhydroxylamine as the main product. Similar results were obtained with 1- and 2-nitropropanes. As the first stage in the reaction, Bevad postulated reaction of the Grignard reagent with the *aci*-form of the nitro-paraffin to give the complex (II), followed by addition of one or two mols. of Grignard reagent to the double bonds:



It was later shown by Zerewitinoff (*Ber.*, 1910, 43, 3593) that primary and secondary nitro-paraffins reacted with methylmagnesium iodide to give slightly less than 1 equivalent of methane, and he also considered that this arose from reaction with the *aci*-nitro-paraffin. Finally Wang (*Trans. Sci. Soc. China*, 1933, 7, 253) made a detailed study of the products obtained by the action of excess of phenylmagnesium bromide on nitromethane. The chief products were phenylmethylhydroxylamine, phenylbenzylhydroxylamine, phenol, and benzene, and a mechanism was formulated, differing in detail from Bevad's theory, but also based on the preliminary formation of a complex of type (II).

All the theories so far advanced are inadmissible since they involve quinquivalent nitrogen; a complex of type (I) as advocated by Moureu would be expected to yield a trialkylamine oxide and not a dialkylhydroxylamine on hydrolysis. The theories advanced by subsequent authors all postulate the preliminary tautomeric change of the nitro-compound to the *aci*-form, though no evidence has been adduced for the occurrence of this change, which normally requires strongly ionising conditions.

The reaction has therefore been re-examined, particular attention being directed to the initial stages. Treatment of nitroethane with 1 mol. of ethylmagnesium bromide at 0° resulted in a vigorous exothermic reaction to form a solid complex which separated from the solution. No gas was evolved during this reaction, but on addition of a further 2 mols. of Grignard reagent the complex largely redissolved and 1 mol. of gas was evolved; this reaction was relatively slow and required heating to drive it to completion. The gas was not identified, but was assumed to be mainly ethane on the evidence of Bevad (*loc. cit.*). The unreacted Grignard reagent, estimated by treating the mixture with water and collecting the evolved gas, amounted to 1 mol. The main liquid product was diethylhydroxylamine. The initial complex was shown by analysis to be an addition product of equimols. of nitroethane and ethylmagnesium bromide, and on reduction with zinc and hydrochloric acid it gave diethylamine in 60% yield. It must therefore have the structure (III). The analogous complex from nitromethane gave methylethylamine on reduction. Similar addition products were obtained by the action of ethylmagnesium bromide on 2-nitropropane and 2-nitro-2-methylpropane, but attempts to reduce them with zinc and hydrochloric acid failed owing to their instability.

It is evident from these results that the first step in the reaction of a nitro-paraffin with ethylmagnesium bromide is the addition of the Grignard reagent to the N=O bond to form a complex of type (III), which is then reduced by a second mol. of Grignard reagent, by a mechanism which is still obscure, to a product which on hydrolysis yields the dialkylhydroxylamine.

EXPERIMENTAL.

The nitro-paraffins used were purified by repeated distillation over phosphoric oxide, followed by thorough washing with water, drying (CaCl_2), and fractionation through a Widmer column. An ethereal solution of ethylmagnesium bromide was filtered through glass wool; the ethylmagnesium bromide content was determined by the method of Gilman *et al.* (*J. Amer. Chem. Soc.*, 1923, **45**, 150), and the solution was then diluted with dry ether to a concentration of 2 g.-mols. per l.

Nitroethane.—(a) A solution of nitroethane (7.5 g.) in pure dry ether (25 c.c.) was placed in a flask cooled in ice-salt and fitted with a mercury-sealed stirrer, reflux condenser, dropping funnel, and system for collecting evolved gases. Ethylmagnesium bromide solution (50 c.c.) was added dropwise to the stirred solution during 1 hour at -5° to 0° . A strongly exothermic reaction took place and a heavy white precipitate was formed, but no gas was evolved. A further 100 c.c. of the Grignard solution was added during 1 hour, by which time the precipitate had largely redissolved and 1400 c.c. of gas had been evolved. The mixture was then refluxed for 1 hour (resulting in the evolution of a further 800 c.c. of gas), cooled in ice, and treated with water (50 c.c.) dropwise at $0-10^\circ$. During the addition of the water, 2200 c.c. of gas were evolved.

(b) Ethylmagnesium bromide solution (50 c.c.) was added dropwise during 1 hour to a stirred solution of nitroethane (7.5 g.) in pure dry ether (100 c.c.) at -5° to 0° . The mixture was then refluxed for 1 hour; no gas was evolved. After cooling, the precipitate was collected, washed with pure dry ether, and dried in a vacuum at 20° , giving a hygroscopic white powder (17.4 g.) which appeared to decompose on treatment with water (Found: Br, 37.25; Mg, 11.65. $\text{C}_4\text{H}_{10}\text{O}_2\text{NBrMg}$ requires Br, 38.45; Mg, 11.64%).

This complex (15 g.) was dissolved in 19% hydrochloric acid (200 c.c.) with ice-cooling, and granulated zinc (30 g.) was added. The reduction was completed by heating on the steam-bath for a short time and the mixture was then cooled in ice, basified with excess of 32% sodium hydroxide solution, and steam-distilled into *n*-hydrochloric acid (100 c.c.); back-titration of the distillate with *n*-sodium hydroxide showed that base equivalent to 45.3 c.c. of *n*-acid (60% theory) had distilled. The neutralised solution was evaporated to dryness and the crude hydrochloride treated with concentrated sodium hydroxide solution. The base, which separated as a volatile oil, reacted with picryl chloride to give a picramide, m. p. $164-165^\circ$, not depressed on admixture with diethyl picramide, m. p. 165° (Found: N, 19.8. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_4\text{N}_4$: N, 19.7%). With phenyl isocyanate the base gave a urea, m. p. $83-84^\circ$, not depressed on admixture with *N*-phenyl-*NN*-diethylurea, m. p. 84° .

(c) Ethylmagnesium bromide solution (750 c.c.) was added during 2 hours to a stirred solution of nitroethane (37.5 g.) in dry ether (100 c.c.) at $0-10^\circ$. The mixture was refluxed for 4 hours, cooled, poured into ice, and steam-distilled until the distillate was only faintly alkaline to brilliant-yellow paper. The distillate was acidified with hydrochloric acid, and the ethereal layer was separated, washed with water, and discarded. The combined aqueous layer and washings were concentrated under reduced pressure, cooled, treated with a large excess of sodium hydroxide, and extracted with ether. The extract was dried (KOH) and fractionated to give diethylhydroxylamine as a colourless oil (20.4 g.), b. p. $50-52^\circ/18$ mm. (Found: equiv., 88.3. Calc. for $\text{C}_4\text{H}_{11}\text{ON}$: equiv., 89), together with small amounts of a volatile base, probably diethylamine, and a high-boiling residue which was not further examined.

Nitromethane.—Nitromethane (6.1 g.) was brought into reaction with ethylmagnesium bromide solution (50 c.c.) by the method (b) described above for nitroethane. This gave the complex (14.5 g.) as a hygroscopic white powder (Found: Br, 41.75; Mg, 12.65. $\text{C}_3\text{H}_5\text{O}_2\text{NBrMg}$ requires Br, 41.25; Mg, 12.4%). Reduction with zinc and hydrochloric acid gave methylethylamine (63% yield), characterised as the picrate, m. p. 96° , and the hydrobromide, m. p. $87-88^\circ$ (Found: Br, 57.2. Calc. for $\text{C}_3\text{H}_7\text{N.HBr}$: Br, 57.15%).

2-Nitropropane.—2-Nitropropane (8.9 g.) was brought into reaction with ethylmagnesium bromide solution (50 c.c.) by the method (b) described above for nitroethane to give the complex (17.2 g.) as a

hygroscopic white powder (Found: Br, 35.3; Mg, 10.65. $C_6H_{11}O_2NBrMg$ requires Br, 36.05; Mg, 10.8%).

Nitro-tert.-butane.—Nitro-*tert.*-butane (10.3 g.) was brought into reaction with ethylmagnesium bromide solution (50 c.c.) by the method (b) described above for nitroethane. This gave a hygroscopic white complex (10 g.) (Found: Br, 34.2; Mg, 10.3. $C_6H_{14}O_2NBrMg$ requires Br, 33.9; Mg, 10.15%).

The author wishes to thank Dr. H. A. Piggott and Mr. J. D. Rose for advice and encouragement during this work.

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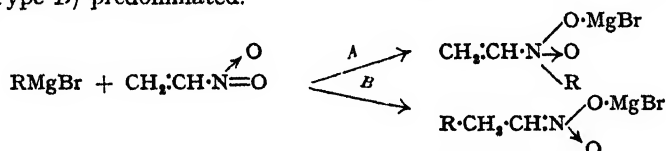
[Received, January 23rd, 1947.]

289. Aliphatic Nitro-compounds. Part X. Action of Grignard Reagents on the α -Nitro-olefins.

By G. D. BUCKLEY.

The reactions of ethyl- and butyl-magnesium bromides with two primary and one secondary α -nitro-olefins have been studied, and, although most of the reaction products have been identified, several points in the mechanism remain obscure. The initial step is a rapid 1:4-addition of the Grignard reagent to the conjugated system $C:C:N=O$ to give a complex which may be decomposed by water to give a nitro-paraffin, or may react with more Grignard reagent to give another complex which on treatment with water yields an oxime. Simultaneously, some 1:2-addition to the nitro-olefin occurs, to give a complex which with water gives basic products, probably dialkylhydroxylamines.

ALTHOUGH organo-magnesium halides readily add to the $N=O$ bond of the nitro-group (see Part IX of this series), Kohler and Stone (*J. Amer. Chem. Soc.*, 1930, 52, 761) have shown that α -nitrostilbene and triphenylnitroethylene react with organo-magnesium halides to give exclusively 1:4-addition products. It was therefore of interest to study the reaction of Grignard compounds with aliphatic nitro-olefins to find whether 1:2-addition (Type A) or 1:4-addition (Type B) predominated.



Addition of ethylmagnesium bromide to an ethereal solution of nitroethylene resulted in immediate polymerisation of the nitro-olefin, but, by reversing the procedure, polymerisation was completely prevented. Slow addition of nitroethylene to 3 mols. of ethylmagnesium bromide at 10–15° resulted in a slow evolution of gas, which was accelerated on boiling the mixture. When 0.66 mol. of gas had been evolved, reaction appeared to be complete, and on treatment of the mixture with water a further 0.75 mol. of gas was evolved, presumably from unreacted Grignard reagent. The acid-insoluble part of the product consisted essentially of two substances, (a) 1-nitrobutane (20% yield) identified by its nitrolic acid reaction (Meyer, *Annalen*, 1875, 175, 120) and by its degradation to *n*-butaldehyde, and (b) hexan-3-one oxime (30% yield) which was readily converted into the corresponding 2:4-dinitrophenylhydrazone (Allen, *J. Amer. Chem. Soc.*, 1930, 52, 2995) and was also reduced to 3-aminohexane. The acid-soluble part of the product was small and boiled over a wide range. It reduced ammoniacal silver nitrate and was hydrogenated to a mixture of non-reducing bases, but no identifiable substance was isolated either before or after hydrogenation. These properties indicated presence of a hydroxylamine.

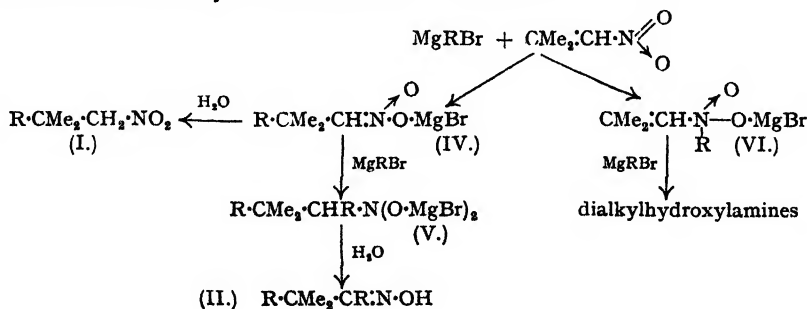
Nitroethylene reacted similarly with excess of *n*-butylmagnesium bromide to give a 43% yield of 1-nitrohexane, a 27.5% yield of a neutral oil, $C_{10}H_{21}ON$, and a small amount of reducing bases. The compound, $C_{10}H_{21}ON$, was assumed to be *decan-5-one oxime* from its reactions and by analogy with the previous example. It was converted into an oily 2:4-dinitrophenylhydrazone which, in agreement with the failure of Bried and Hennion (*J. Amer. Chem. Soc.*, 1938, 60, 1718) to prepare crystalline derivatives of decan-5-one, could not be obtained solid; catalytic reduction gave 5-aminodecane.

Since 1-nitro-2-methylprop-1-ene is not polymerised by Grignard reagents, it was possible to

study more closely the course of the reaction of ethylmagnesium bromide with this nitro-olefin. This reaction of the first mol. of Grignard reagent was strongly exothermic and took place readily at 0° without evolution of gas. Further Grignard reagent reacted only slowly at 0°, but more readily at 15–20°. The reaction was mildly exothermic, and 1 mol. of gas was evolved, 3 mols. of Grignard reagent being consumed in all. The gas had the properties of a saturated hydrocarbon, and on combustion was found to be chiefly ethane. The products were 1-nitro-2:2-dimethylbutane (20%) (which gave the characteristic primary nitro-compound reaction and on reduction afforded the known 1-amino-2:2-dimethylbutane), and a crystalline solid, $C_8H_{13}ON$ (28%), which failed to react with 2:4-dinitrophenylhydrazine or 2:4-dinitrophenylsemicarbazide and was hydrogenated only with difficulty to a primary amine, $C_8H_{15}N$; by analogy with the previous examples it is believed to be 3:3-dimethylhexan-4-one oxime (II; $R = Et$), and the derived amine, 4-amino-3:3-dimethylhexane, the unreactivity of the oxime being attributed to steric factors.

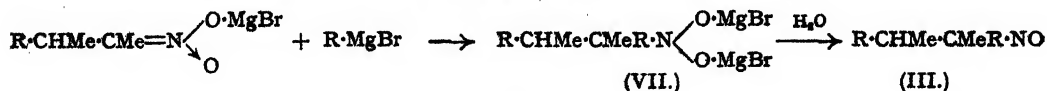
Addition of ethylmagnesium bromide to 2-nitrobut-2-ene gave polymers as in the case of nitroethylene, but this was again overcome by adding the nitro-olefin to excess of the Grignard reagent. Gaseous hydrocarbon (0.75 mol.) was evolved and 2.5 mols. of ethylmagnesium bromide were consumed. An acid-soluble fraction consisting of reducing bases similar to those obtained from the primary nitro-olefin was isolated, and the neutral fraction was separated into an oil, $C_6H_{13}O_2N$ (26%), an oil, $C_8H_{17}ON$ (8%), and a large amount of non-volatile tar. The compound $C_8H_{13}O_2N$, which gave the nitrole reaction characteristic of a secondary nitro-group (Meyer, *loc. cit.*) and yielded a primary amine on reduction, was 2-nitro-3-methylpentane. The oil, $C_8H_{17}ON$, was colourless and contained one active hydrogen atom (Zerewitinoff); this excluded the possibility that it had the nitroso-structure (III; $R = Et$). It did not give the Meyer test for a nitro-paraffin, but on reduction it gave an amine, $C_8H_{19}N$. It must therefore be an oxime although, like the isomeric 3:3-dimethylhexan-4-one oxime, it failed to react with 2:4-dinitrophenylhydrazine or 2:4-dinitrophenylsemicarbazide.

On the basis of these results it is possible to build up a fairly complete picture of the course of the reaction of a Grignard reagent with a primary nitro-olefin, as shown in the scheme below for the reaction of ethylmagnesium bromide with 1-nitro-2-methylpropene. The initial step is addition (chiefly 1:4) of the Grignard reagent to the conjugated system to produce a complex (IV) which on hydrolysis gives the nitro-paraffin (I), but since (IV) contains the system $C=N \rightarrow O$, addition of a second mol. of Grignard reagent occurs to give the complex (V) which on hydrolysis yields the oxime (II). The formation of reducing bases and of ethane can be explained only by the assumption that part of the nitro-olefin undergoes 1:2-addition of Grignard reagent to give a complex (VI) which reacts with more Grignard reagent to give dialkylhydroxylamines; this process is analogous to the formation of dialkylhydroxylamines by the action of Grignard reagents on nitro-paraffins (this series, Part IX; Bevad, *Ber.*, 1907, 40, 3065). Unfortunately, the nitro-olefin reaction produces mixtures of bases of so complex a nature and in such small amount that it has not been possible to isolate pure products which would establish with certainty the occurrence of 1:2-addition.



The secondary nitro-olefin underwent a similar series of reactions. The formation of 2-nitro-3-methylpentane in the reaction of 2-nitrobut-2-ene with ethylmagnesium bromide is clear evidence of 1:4-addition, and the isolation of reducing bases and the formation of a hydrocarbon again point to the occurrence of some 1:2-addition. The nature of the reaction of the 1:4-addition complex of the secondary nitro-olefin with more Grignard reagent is obscure; if it followed the same course as for the primary nitro-olefins the product would be a nitroso-compound (III). However, as stated above, although a product of the same empirical

formula as (III) was isolated, it appeared to be an oxime, which may result from a rearrangement of (II) or of its complex (VII). Such a rearrangement might also explain the extensive tar formation, which was observed only in the case of the secondary nitro-olefin.



EXPERIMENTAL.

Microanalyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

Nitroethylene and Ethylmagnesium Bromide.—A solution of nitroethylene (Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) (11.2 g.) in dry ether (60 c.c.) was added during 1 hour to a stirred solution of ethylmagnesium bromide (from 50 g. ethyl bromide) in ether (250 c.c.) at 10–15°, and the mixture was then stirred and refluxed for 2 hours; gas evolution had then ceased. This gas (2100 c.c. at N.T.P.) did not react with bromine and did not liquefy on cooling to –80°. The mixture was cooled in ice, and water (100 c.c.) was added dropwise; a further 2300 c.c. of gas were evolved. The mixture was acidified to Congo-red with dilute sulphuric acid, separated, and the aqueous layer, made strongly alkaline with sodium hydroxide, was extracted with ether in a continuous extractor. The extract was dried (NaOH) and distilled, giving a strongly basic oil (4.8 g.) which boiled over a wide range under reduced pressure and reduced ammoniacal silver nitrate. Catalytic hydrogenation in the presence of Raney nickel gave a non-reducing basic oil which distilled over a wide range and from which no crystalline derivative could be prepared.

The ethereal solution containing the acid-insoluble products was dried and distilled. Two fractions were isolated: (1) b. p. 50–65°/30 mm., and (2) b. p. 90–100°/30 mm. Redistillation of fraction (1) gave 1-nitrobutane (3.2 g.) as a colourless oil, b. p. 150–152°, which gave a positive test for the presence of a primary nitro-group (Meyer, *loc. cit.*). A solution of the nitro-compound in dilute aqueous sodium hydroxide, run into excess of 20% sulphuric acid at 10–15°, gave *n*-butaldehyde (2:4-dinitrophenylhydrazones, m. p. and mixed m. p. with an authentic specimen, 126°).

Redistillation of fraction (2) gave hexan-3-one oxime (4.7 g.) as a colourless oil, b. p. 98–100°/30 mm. (Found: N, 12.0. Calc. for $\text{C}_6\text{H}_{13}\text{ON}$: N, 12.2%). The oxime, with 2:4-dinitrophenylhydrazine in 2*N*-hydrochloric acid, gave hexan-3-one 2:4-dinitrophenylhydrazone as red needles, m. p. 128–129°; Allen (*loc. cit.*) gives m. p. 129° (Found: C, 50.95; H, 5.5; N, 20.4. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{N}_4$: C, 51.4; H, 5.7; N, 20.0%).

3-Aminohexane. A solution of hexan-3-one oxime (3.5 g.) in methyl alcohol (35 c.c.) was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased. The filtered solution was acidified with hydrochloric acid and evaporated to dryness, and the residue after being washed with acetone afforded 3-aminohexane hydrochloride, m. p. 225–226°. Bevad (*J. pr. Chem.*, 1901, 63, 230) gives m. p. 227–229° (Found: Cl, 25.2. Calc. for $\text{C}_6\text{H}_{13}\text{N.HCl}$: Cl, 25.9%). The hydrochloride with potassium cyanate in boiling aqueous solution gave 3-ureidohexane, m. p. 150–151° (Found: C, 58.65; H, 11.3; N, 18.9. $\text{C}_6\text{H}_{13}\text{ON}_2$ requires C, 58.35; H, 11.1; N, 19.35%).

Nitroethylene and *n*-Butylmagnesium Bromide.—Nitroethylene (14.6 g.) was brought into reaction with a Grignard solution, prepared from *n*-butyl bromide (75.5 g.), as described above for ethylmagnesium bromide. When reaction was complete the mixture was cooled in ice, decomposed by cautious addition of aqueous acetic acid (150 c.c. of 20%), and separated. The ethereal solution was washed with dilute sodium hydrogen carbonate solution, dried, and distilled. This gave two fractions: (1) b. p. 84°/21 mm., and (2) b. p. 120–123°/12 mm. Fraction (1), a colourless, sweet-smelling oil which gave the nitrolic acid reaction, was 1-nitrohexane (Found: C, 55.15; H, 9.85; N, 10.65. Calc. for $\text{C}_6\text{H}_{13}\text{O}_2\text{N}$: C, 54.95; H, 9.9; N, 10.7%). Hydrolysis with concentrated hydrochloric acid at 160° in a sealed tube for 12 hours gave hexoic acid, which was characterised as the amide, m. p. 98°, and the anilide, m. p. 95°. Fraction (2) was a colourless oil, decan-5-one oxime (Found: C, 70.5; H, 12.45; N, 7.95. $\text{C}_{10}\text{H}_{21}\text{ON}$ requires C, 70.2; H, 12.3; N, 8.2%).

***n*-Hexylamine.** A solution of 1-nitrohexane (5.5 g.) in methyl alcohol (80 c.c.) was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased. The filtered solution was acidified with hydrochloric acid and evaporated to dryness, giving the hydrochloride (2.25 g.) which, after being washed with acetone, had m. p. 217–218° (Found: Cl, 25.75. Calc. for $\text{C}_6\text{H}_{13}\text{N.HCl}$: Cl, 25.9%). With potassium cyanate in boiling aqueous solution the hydrochloride gave *n*-hexylurea, m. p. 108° (cf. Norstedt and Wahlforss, *Ber.*, 1892, 25, ref. 637).

5-Aminodecane. 5-Decanone oxime (3 g.) was dissolved in methyl alcohol and hydrogenated over Raney nickel at 20°/1 atm. After filtration and evaporation, 5-aminodecane was obtained as an oil which on treatment with phenyl isocyanate gave 5-phenylureidodecane, m. p. 129–130°, colourless needles from acetic acid (Found: C, 73.85; H, 10.1; N, 10.15. $\text{C}_{11}\text{H}_{23}\text{ON}_2$ requires C, 73.9; H, 10.15; N, 10.15%).

1-Nitro-2-methylprop-1-ene and Ethylmagnesium Bromide.—1-Nitro-2-methylprop-1-ene (25 g.; Levy and Scaife, in the press) was dissolved in dry ether (25 c.c.) and cooled to 0°. A solution of ethylmagnesium bromide (125 c.c.) was added during 1 hour with stirring at 0–5°; no gas was evolved. The temperature was raised to 15° and a further 475 c.c. of the Grignard solution were added during 1 hour at 15–25°; 5.5 l. of ethane were evolved. The mixture was refluxed for 12 hours, cooled and treated dropwise with water (125 c.c.) which liberated a further 5.5 l. of ethane. After acidification with dilute hydrochloric acid, the mixture was separated and the aqueous portion was made strongly alkaline with sodium hydroxide and steam-distilled. From the distillate was obtained by isolation with ether a small amount of a strongly basic oil which reduced ammoniacal silver nitrate.

The ethereal solution, containing the acid-insoluble products, was dried and distilled, giving two

fractions. Fraction (1) (6.2 g.), a colourless, sweet-smelling oil, b. p. 70°/25 mm., which gave the nitrolic acid reaction, was 1-nitro-2:2-dimethylbutane (I; R = Et) (Found: C, 54.75; H, 9.8; N, 10.8. $C_8H_{15}O_2N$ requires C, 54.95; H, 9.9; N, 10.7%). Fraction (2) (10.1 g.), a colourless crystalline solid, b. p. 100°/25 mm., was 3:3-dimethylhexan-4-one oxime (II; R = Et), m. p. 42–43°, from light petroleum (b. p. 40–60°) (Found: C, 67.55; H, 12.1; N, 9.65. $C_{12}H_{21}ON$ requires C, 67.15; H, 11.9; N, 9.8%).

1-Amino-2:2-dimethylbutane. A solution of the nitro-compound (4.3 g.) in methyl alcohol (50 c.c.) was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased. The filtered solution was fractionally distilled, giving the amine as a colourless oil (2.3 g.), b. p. 110–115° (Found: equiv., 99.9. Calc. for $C_8H_{17}N$: equiv. 101). The picramide, yellow needles from alcohol, had m. p. 80° (Found: C, 46.25; H, 5.25; N, 17.85. Calc. for $C_{12}H_{19}O_6N_4$: C, 46.15; H, 5.1; N, 18.0%). The benzenesulphonyl derivative had m. p. 59° (Found: N, 6.05. Calc. for $C_{13}H_{19}O_2NS$: N, 5.8%). Drake, Kline, and Rose (*J. Amer. Chem. Soc.*, 1934, 56, 2079) give m. p. 88–88.5° for the picramide and m. p. 59–59.5° for the benzenesulphonyl derivative of 1-amino-2:2-dimethylbutane.

4-Amino-3:3-dimethylhexane. A solution of 3:3-dimethylhexan-4-one oxime (6.8 g.) in methyl alcohol (70 c.c.) was stirred in an autoclave with Raney nickel and hydrogen at 100°/100 atm. until absorption ceased. The filtered solution was acidified with hydrochloric acid and evaporated to dryness. The product was dissolved in a little water, washed with ether, basified with sodium hydroxide, extracted with ether, and the extract dried (KOH). Distillation gave 4-amino-3:3-dimethylhexane (3.3 g.) as a colourless oil, b. p. 152° (Found: equiv., 130.7. $C_8H_{19}N$ requires equiv., 129). Reaction with phenyl isocyanate in dry ether gave 4-phenylureido-3:3-dimethylhexane, m. p. 157–158°, colourless needles from acetic acid (Found: C, 72.45; H, 9.65; N, 11.35. $C_{15}H_{24}ON_2$ requires C, 72.6; H, 9.7; N, 11.3%). With picryl chloride in alcohol the base gave 4-picrylamino-3:3-dimethylhexane, m. p. 60°, orange plates from alcohol (Found: C, 49.6; H, 5.5; N, 16.65. $C_{14}H_{20}O_6N_4$ requires C, 49.4; H, 5.9; N, 16.45%).

2-Nitrobut-2-ene and Ethylmagnesium Bromide.—2-Nitrobut-2-ene (62 g.; this series, Part III) was brought into reaction, under the conditions described above for nitroethylene, with a Grignard solution prepared from ethyl bromide (218 g.); 10 l. of ethane were evolved. Distillation of the acid-insoluble portion of the product under reduced pressure left a large non-volatile tarry residue, and repeated fractionation separated the distillate into two fractions. The acid-soluble portion (12 g.), fraction (3), was isolated by treatment of the aqueous solution with sodium hydroxide, followed by extraction with ether in a continuous extractor. Fraction (1) (20.3 g.), a colourless oil, b. p. 68–70°/25 mm., which gave the μ -nitrolic acid reaction (Meyer, *loc. cit.*), was 2-nitro-3-methylpentane (Found: C, 54.75; H, 9.6; N, 10.8. $C_8H_{15}O_2N$ requires C, 54.95; H, 9.9; N, 10.7%). Fraction (2) (7 g.) was a colourless oil, b. p. 98–100°/20 mm., which did not give the Meyer nitro-paraffin test and did not react with 2:4-dinitrophenylhydrazine in acid solution (Found: C, 67.8; H, 11.8; N, 10.1; active H (Zerewitinoff) 0.63. $C_8H_{15}ON$ requires C, 67.15; H, 11.9; N, 9.8; 1 active H, 0.7%). On reduction with Raney nickel and hydrogen in methyl alcohol at 100°/100 atm. fraction (2) gave a colourless basic oil, b. p. 157–158° (Found: equiv., 130.2. $C_8H_{19}N$ requires equiv., 129), which gave a hydrochloride of indefinite m. p., readily soluble in alcohol, acetone, and ether (Found: Cl, 21.65. $C_8H_{19}N.HCl$ requires Cl, 21.45%).

Fraction (3) was a strongly basic oil, boiling over a wide range (40–110°/10 mm.); it reduced ammoniacal silver nitrate and absorbed hydrogen in the presence of a nickel catalyst, but no crystalline derivatives could be obtained from the resulting mixture of amines.

2-Amino-3-methylpentane. A solution of 2-nitro-3-methylpentane (10 g.) in methyl alcohol (100 c.c.) was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased. The filtered solution was distilled, giving 2-amino-3-methylpentane as a colourless oil, b. p. 105–107° (Found: equiv., 102.7. $C_8H_{15}N$ requires equiv., 101). With picryl chloride it gave a picramide, m. p. 58–59° (Found: C, 46.3; H, 5.1; N, 17.7. $C_{13}H_{19}O_6N_4$ requires C, 46.15; H, 5.1; N, 18.0%).

The author wishes to acknowledge the interest and advice of Dr. H. A. Piggott and Mr. J. D. Rose in this work.

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[Received, January 23rd, 1947.]

290. Aliphatic Nitro-compounds. Part XI. Preparation of Nitro-paraffins by 1:4-Addition of Organometallic Halides to α -Nitro-olefins.*

By GERARD D. BUCKLEY and ERIC ELLERY.

A series of hitherto unknown or inaccessible nitro-paraffins has been prepared by 1:4-addition of alkyl- or aryl-magnesium halides or alkylzinc halides to α -nitro-olefins. By carrying out the reaction below 10° and avoiding excess of organometallic halide secondary reactions are almost completely suppressed, but the yield of nitro-paraffin never exceeds 65% and is frequently less, apparently owing to the simultaneous occurrence of some 1:2-addition.

THE formation of nitro-paraffin derivatives in high yield by the action of Grignard reagents on di- and tri-phenylnitroethylenes has been described by Kohler and Stone (*J. Amer. Chem. Soc.*, 1930, 52, 761). Under similar conditions simpler nitro-olefins yield a complex mixture of

* Cf. B.P. 571,804.

products of which the nitro-paraffin forms only a small proportion (Part X of this series). The nitro-paraffins are formed by 1 : 4-addition of the Grignard reagent to the conjugated system and the by-products arise partly from 1 : 2-addition and partly from the action of excess of Grignard reagent on the initial addition products.

The results described in Part X indicate that the initial addition occurs much more readily than the subsequent reactions, and it has now been found that, by working at low temperatures and avoiding excess of Grignard reagent, secondary reactions are suppressed, and nitro-paraffins are obtained as the main products. The reaction has been carried out on a variety of nitro-olefins and organomagnesium halides (and one alkylzinc halide) and appears to be quite general. The yields are frequently poor, but are probably capable of considerable improvement, since 60–65% yields were obtained consistently in the only two examples in which any attempt was made to determine the optimum conditions of reaction and isolation, *viz.*, the reaction of *n*-butylmagnesium bromide with nitroethylene and of ethylmagnesium bromide with 1-nitro-2-methylprop-1-ene.

In the two cases in which alkylmagnesium iodides were used small amounts of crystalline by-products were formed, but owing to the smallness of the amounts available they were not further investigated; no trace of these compounds was found when the corresponding bromides were used.

EXPERIMENTAL.

Microanalyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

1-Nitro-2 : 2-dimethylbutane.—(a) *From ethylmagnesium bromide.* A solution of ethylmagnesium bromide, prepared from ethyl bromide (48 g.) in ether (200 c.c.), was added during 1 hour to a stirred solution of 1-nitro-2-methylprop-1-ene (40 g.; Levy and Scaife, in the press) in pure, dry ether (400 c.c.), the temperature being held at 0–10°. The mixture was refluxed for 1 hour, cooled in ice, and treated cautiously with a solution of acetic acid (20 c.c.) in water (160 c.c.). The ethereal layer was washed with dilute sodium carbonate solution, dried, and distilled, giving 1-nitro-2 : 2-dimethylbutane (30.2 g.; 60% of theory) as a sweet-smelling oil, b. p. 168–170° (cf. Part X).

(b) *From ethylmagnesium iodide.* To an ice-cold, stirred solution of ethylmagnesium iodide, prepared in the usual manner from ethyl iodide (78 g.) in ether (200 c.c.), was added 1-nitro-2-methylprop-1-ene (34 g.) in ether (40 c.c.) during 1 hour at 0–10°. The mixture was stirred at 20° for 2 hours and worked up as before. Distillation of the crude product gave 25.3 g. (57.5% theory) of 1-nitro-2 : 2-dimethylbutane, b. p. 168–170°. The undistilled residue was crystallised from alcohol, giving colourless granules (0.4 g.) of an unidentified product, m. p. 182° (Found : C, 52.25; H, 7.55; N, 14.75. $C_8H_{14}O_2N_2$ requires C, 51.6; H, 7.5; N, 15.05%).

(c) *From ethylzinc iodide.* A solution of ethylzinc iodide in dry toluene, prepared from ethyl iodide (47 g.), was stirred at 0–10° and treated with a solution of 1-nitro-2-methylprop-1-ene (15 g.) in pure, dry ether (15 c.c.) during 1 hour. The mixture was then stirred at 50° for 3 hours, poured into ice, and treated with glacial acetic acid (20 c.c.). The organic layer was separated, dried, and fractionated to give 1-nitro-2 : 2-dimethylbutane (5.6 g.), b. p. 78–80°/30 mm.

Nitro-norbornane.—A solution of methylmagnesium iodide, prepared from methyl iodide (71 g.), was brought into reaction with 1-nitro-2-methylprop-1-ene (34 g.) as described above for ethylmagnesium iodide. After working up in the usual manner, the crude product was distilled, giving *nitro-norbornane* (16.2 g.; 42%) as a colourless oil, b. p. 77–78°/65 mm. (Found : C, 51.65; H, 9.35; N, 11.95. $C_8H_{11}O_2N$ requires C, 51.3; H, 9.4; N, 11.95%). The non-volatile residue crystallised on cooling and was purified by recrystallisation from alcohol and benzene, giving colourless prisms, m. p. 144° (Found : C, 46.8; H, 7.8; N, 13.05. $C_8H_{10}O_2N$ requires C, 47.05; H, 7.85; N, 13.7%).

1-Nitro-2 : 2 : 3 : 3-tetramethylpentane.—A solution of *tert*-amylmagnesium chloride, prepared from *tert*-amyl chloride (21.3 g.) by the method of Whitmore and Badertscher (*J. Amer. Chem. Soc.*, 1933, **55**, 1559), was brought into reaction with 1-nitro-2-methylprop-1-ene (10 g.) as described above for ethylmagnesium iodide. After isolation as before, the crude product was fractionated to give a colourless oil (6.5 g.), b. p. 102–105°/11 mm., having a camphor-like odour (Found : C, 62.55; H, 10.65; N, 8.45. $C_{12}H_{21}O_2N$ requires C, 62.45; H, 10.95; N, 8.1%).

$\alpha\alpha\beta\beta$ -Tetramethylvaleric Acid.—1-Nitro-2 : 2 : 3 : 3-tetramethylpentane (6 g.) was mixed with concentrated aqueous hydrochloric acid (20 c.c.) and heated in a sealed tube at 150° for 6 hours. The product was diluted with water and extracted with ether, and the ethereal solution washed thoroughly with dilute aqueous sodium carbonate. The alkaline extract was acidified with dilute sulphuric acid, extracted with ether, and the dried ethereal solution was distilled, giving $\alpha\alpha\beta\beta$ -tetramethylvaleric acid, b. p. 122°/15 mm., m. p. 89–90° [from light petroleum (b. p. 40–60°)] (Found : C, 68.8; H, 11.4; equiv., 158. $C_8H_{15}O_4$ requires C, 68.35; H, 11.4%; equiv., 158).

1-Nitro-2 : 2-dimethylpent-4-ene.—Allyl bromide (41 g.) in dry ether (250 c.c.) was converted into the Grignard reagent by the method of Gilman and McGlumphy (*Bull. Soc. chim.*, 1928, **43**, 1322), and the resulting solution filtered through glass wool and cooled to 0°. A solution of 1-nitro-2-methylprop-1-ene (20 g.) in dry ether (50 c.c.) was then added with stirring during 1 hour at 0–10°. After being stirred at 20° for 2 hours the mixture was poured into ice, treated with acetic acid (25 c.c.), and separated. The ethereal solution was dried and distilled under reduced pressure, giving much unchanged 1-nitro-2-methylprop-1-ene and a small yield (6.5 g.) of 1-nitro-2 : 2-dimethylpent-4-ene, b. p. 77°/20 mm. (Found : N, 9.7. $C_7H_{13}O_2N$ requires N, 9.8%). This was a pleasant-smelling oil, which gave the Meyer test for a primary nitro-compound, and reacted with bromine in carbon tetrachloride to give a liquid bromo-derivative.

1-Nitrohexane.—Nitroethylene (21 g.) dissolved in dry ether (100 c.c.) was added during 1 hour to a stirred solution of *n*-butylmagnesium bromide (0.4 g. mol.) in ether (250 c.c.). A vigorous exothermic reaction ensued, and the temperature was maintained below 0° with a freezing mixture; when the addition was complete the mixture was stirred for 1 hour at 20° and the complex decomposed by cautious addition of a solution of acetic acid (48 c.c.) in water (240 c.c.). After being stirred for a further 45 minutes, the mixture was steam-distilled, the ethereal layer of distillate separated, dried, and distilled, giving 38.6 g. (65%) of 1-nitrohexane, b. p. 84°/21 mm.; n_D^{20} 1.4270 (cf. Part X of this series) (Found : N, 10.65. Calc. for $C_6H_{13}O_2N$: N, 10.7%).

2-Nitro-3-methylpentane.—2-Nitrobut-2-ene (50 g.; this series, Part III) was dissolved in dry ether (250 c.c.) and brought into reaction with a solution of ethylmagnesium bromide (0.75 g. mol.) in ether (375 c.c.) as described above for the preparation of 1-nitrohexane. After working up in the usual way 2-nitro-3-methylpentane (27.7 g.; 42.5%) was obtained as a colourless oil, b. p. 70–73°/20 mm.; n_D^{20} 1.4320 (cf. Part X of this series) (Found : N, 10.8. Calc. for $C_6H_{13}O_2N$: N, 10.7%).

2-Nitropentane.—2-Nitroprop-1-ene (17.4 g.; this series, Part I) dissolved in dry ether (60 c.c.) was brought into reaction with ethylmagnesium bromide (from 22 g. of ethyl bromide) in ether (100 c.c.) as described above for the preparation of 1-nitrohexane. After working up in the usual way the crude distillate (b. p. 40–60°/12 mm.) was washed with aqueous sodium hydrogen sulphite to remove unchanged 2-nitroprop-1-ene, dried, and fractionated, giving a colourless oil, b. p. 148–150°. 2-Nitropentane is a pleasant-smelling oil, soluble in dilute aqueous sodium hydroxide, which gives the Meyer test for a secondary nitro-compound (Found : C, 51.65; H, 9.7; N, 11.8. $C_5H_{11}O_2N$ requires C, 51.3; H, 9.4; N, 11.95%). Reduction of 2-nitropentane (3.5 g.) in methyl alcohol with hydrogen in the presence of Raney nickel in the usual way gave 2-aminopentane, isolated as the hydrochloride (3.4 g.). Reaction of the base with phenyl isocyanate gave the phenylurea, m. p. 119–120°, colourless plates from aqueous alcohol. Mailhe (*Bull. Soc. chim.*, 1905, **33**, 966) gives m. p. 120° for *N*-phenyl-*N'*- α -methylbutylurea (Found : N, 13.6. Calc. for $C_{12}H_{18}ON_2$: N, 13.6%).

2-Nitro-3-methylpentadecane.—A solution of dodecylmagnesium bromide (from 55 g. of dodecyl bromide) in dry ether (250 c.c.) was added during 1 hour to a stirred solution of 2-nitrobut-2-ene (30 g.) in dry ether (150 c.c.) at 0–5°. The mixture was refluxed for 1 hour, cooled, and treated cautiously with aqueous acetic acid (120 c.c. of 20%). The mixture was stirred until all the magnesium salts had dissolved, and the ethereal layer was dried, concentrated, and the residue repeatedly fractionated in a vacuum to give the nitro-compound (20 g.) as a pale yellow oil, b. p. 111–115°/0.06 mm. (Found : C, 71.0; H, 12.1; N, 5.85. $C_{16}H_{33}O_2N$ requires C, 70.85; H, 12.2; N, 5.2%). This gave the Meyer test for a secondary nitro-compound and formed a crystalline sodium salt on treatment with alcoholic sodium hydroxide.

2-Amino-3-methylpentadecane.—The nitro-compound (10 g.) was catalytically reduced in methyl alcohol in the presence of Raney nickel at ordinary temperature and pressure. Distillation of the filtered solution gave the amine (5.5 g.) as a colourless oil, b. p. 158–160°/11 mm. (Found : equiv., 237. $C_{16}H_{33}N$ requires equiv., 241). An aqueous solution of the hydrochloride, on being boiled with excess potassium cyanate, deposited colourless crystals of 2-ureido-3-methylpentadecane, m. p. 122–123° (from alcohol) (Found : C, 71.4; H, 12.4; N, 9.9. $C_{17}H_{35}ON_2$ requires C, 71.8; H, 12.7; N, 9.9%).

2-Nitroisopropylcyclohexane.—cycloHexylmagnesium bromide (from 81.5 g. of cyclohexyl bromide) was brought into reaction with 1-nitroprop-1-ene (29 g.; this series, Part I) as described above for the preparation of 1-nitrohexane. After decomposition of the complex the ethereal layer was concentrated and the residue dissolved in alcohol (200 c.c.), treated with aqueous sodium hydroxide (35 c.c. of 32%) at 0–5°, the solution diluted with water (400 c.c.), and washed with ether. The aqueous solution was made acid to Congo-red with concentrated hydrochloric acid at 0–5° and extracted with ether. The extract was dried and distilled, giving 2-nitroisopropylcyclohexane as a pale yellow oil, b. p. 122°/16 mm. (Found : C, 63.4; H, 9.7; N, 8.2. $C_9H_{17}O_2N$ requires C, 63.15; H, 9.95; N, 8.2%).

2-Nitro-3-phenylbutane.—Phenylmagnesium bromide (from 51 g. of bromobenzene) was brought into reaction with 2-nitrobut-2-ene (20 g.) as described above for the preparation of 1-nitrohexane. After isolation in the usual manner the product was distilled under reduced pressure, giving impure 2-nitro-3-phenylbutane (22.5 g.), b. p. 118–120°/13 mm. This material, which appeared to contain some diphenyl, was not further purified but was reduced with hydrogen in methyl alcohol in the presence of Raney nickel at ordinary temperature and pressure. The filtered solution was acidified with hydrochloric acid and evaporated to dryness on the steam-bath, the residue dissolved in water, and washed with ether. The aqueous solution was then basified with concentrated sodium hydroxide and extracted with ether. The extract was dried (KOH) and distilled, giving the amine as a colourless oil (10.7 g.), b. p. 87°/12 mm. (Found : equiv., 147. $C_{10}H_{15}N$ requires equiv., 149). Reaction with picryl chloride gave 2-picrylamino-3-phenylbutane, m. p. 119–120°, yellow plates from alcohol (Found : N, 15.65. $C_{16}H_{15}O_6N_3$ requires N, 15.55%).

2-Nitro-3-phenylheptane.—2-Nitro-1-phenylprop-1-ene (32 g.; Alles, *J. Amer. Chem. Soc.*, 1932, **54**, 272) dissolved in dioxan (120 c.c.) was added during 1 hour to a stirred ethereal solution (150 c.c.) of butylmagnesium bromide (prepared from 42 g. of butyl bromide) at 0–5°. The mixture was stirred at 20° for 1 hour and the product isolated in the usual way. Distillation gave impure 2-nitro-3-phenylheptane (29 g.), b. p. 62–90°/0.02 mm., which was not further purified, but was reduced with hydrogen and Raney nickel in methyl alcohol. The filtered solution was acidified with hydrochloric acid and evaporated to dryness on the steam-bath; the residue was dissolved in water and washed with ether. The aqueous solution was basified with sodium hydroxide and the amine isolated with ether. Distillation gave 2-amino-3-phenylheptane as a colourless oil, b. p. 114–115°/9 mm. (Found : equiv., 191. $C_{13}H_{21}N$ requires equiv., 191). This material, apparently a mixture of stereoisomerides, gave a hydrochloride of indefinite m. p. (Found : Cl, 15.5. $C_{13}H_{21}N.HCl$ requires Cl, 15.6%). Attempts to prepare crystalline derivatives with benzoyl chloride, phenyl isocyanate, picryl chloride, and nitrourea failed.

1-Nitro-2-(2-furyl)hexane.—A solution of 1-nitro-2-(2-furyl)ethylene (14 g.; Thiele and Landers, *Annalen*, 1909, **369**, 303) in dioxan (70 c.c.) was added during 1 hour at 0–10° to a stirred solution (150 c.c.) of *n*-butylmagnesium bromide prepared from *n*-butyl bromide (34.5 g.). The solution was stirred.

at 20° for 18 hours, poured on ice, and the product isolated in the usual way, giving 1-nitro-2-(2-furyl)-hexane as a pale yellow oil (6.5 g.), b. p. 78—82°/0.4 mm. (Found : N, 7.2. $C_{10}H_{18}O_2N$ requires N, 7.1%).

1-Nitro-2-benzylcyclohexane.—An ethereal solution of benzylmagnesium chloride (prepared from 34 g. of benzyl chloride) was brought into reaction with 1-nitrocyclohexene (32 g.; Wieland *et al.*, *Annalen*, 1921, 424, 71) as described above for the preparation of 1-nitrohexane. Distillation of the product gave impure 1-nitro-2-benzylcyclohexane (23.5 g.), b. p. 91—115°/0.04 mm. This material, apparently containing 1 : 2-diphenylethane, was hydrogenated in the usual way over Raney nickel without further purification. The resulting amine was purified through its hydrochloride and finally distilled, giving a colourless oil (12.5 g.), b. p. 138—140°/11 mm. (Found : equiv., 191. Calc. for $C_{15}H_{21}N$: equiv., 189). This base, apparently a mixture of isomerides, was dissolved in benzene (50 c.c.) and shaken with 2*N*-hydrochloric acid (70 c.c.). After 45 minutes, the precipitated hydrochloride was collected; this appeared to be still a mixture, and no pure derivatives could be isolated from it. On standing overnight the mother liquor deposited a second precipitate which was collected and crystallised repeatedly from 2*N*-hydrochloric acid to give pure *cis*-2-benzylcyclohexylamine hydrochloride, m. p. 224°. This formed an acetyl derivative, m. p. 116°, and a benzoyl derivative, m. p. 155° (Found : C, 82.5; H, 8.25; N, 4.7. Calc. for $C_{20}H_{23}ON$: C, 81.9; H, 7.85; N, 4.8%). No m. p. depression was observed on admixture of these derivatives with authentic specimens prepared according to Schöpf and Boettcher (*Annalen*, 1926, 448, 1).

The authors thank Dr. H. A. Piggott and Mr. J. D. Rose for their interest and encouragement in this work.

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[Received, January 23rd, 1947.]

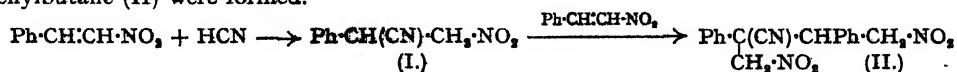
291. Aliphatic Nitro-compounds. Part XII. Preparation and Reduction of 2-Nitroalkyl Cyanides.*

By G. D. BUCKLEY, R. L. HEATH, and J. D. ROSE.

Interaction of alkali-metal cyanides (or mixtures of these with hydrogen cyanide) and α -nitro-olefins yields 2-nitroalkyl cyanides. 2-Nitro-1-methylisopropyl cyanide, formed in 90% yield from 1-nitro-2-methylprop-1-ene and hydrogen cyanide-potassium cyanide, yields on catalytic reduction only minor quantities of the expected 2-amino-1-methylisopropyl cyanide and 1 : 3-diamino-2 : 2-dimethylpropane, the major products being 2-amino-1-methylisobutyramide and 5 : 5-dimethyl-2-(1-carbamylisopropyl)hexahydropyrimidine (III). 2-Nitropropyl cyanide, 2-nitroisopropyl cyanide, and 2-nitro-1-methylpropyl cyanide on reduction yield, in addition to the amino-cyanides, some of the corresponding amino-amides.

In connection with a general programme of work on the addition reactions of the α -nitro-olefins, a study of the formation of 2-nitroalkyl cyanides by interaction of metallic cyanides (or mixtures of these with hydrogen cyanide) with α -nitro-olefins was undertaken. The reduction of the nitroalkyl cyanides was investigated as a potential technical route to certain 1 : 3-diamines and β -amino-acids required for synthetic work in another connection.

The literature contains only one reference to the interaction of a metal cyanide with an α -nitro-olefin. Hollemann (*Rec. Trav. chim.*, 1904, 23, 283) showed that by interaction of β -nitrostyrene and potassium cyanide, two stereoisomerides of 1 : 4-dinitro-2-cyano-2 : 3-diphenylbutane (II) were formed.



The primary reaction in the formation of (II) must be the addition of hydrogen cyanide to the nitro-olefin, giving 2-nitro-1-phenylethyl cyanide (I), which by further reaction with nitrostyrene affords (II).

Interaction of 1- and 2-nitroprop-1-ene with aqueous potassium cyanide gave 2-nitroisopropyl cyanide and 2-nitro-n-propyl cyanide, respectively, but the yields were poor (10—15%), much of the olefin being lost by polymerisation in the alkaline reaction medium. 2-Nitrobut-2-ene, which polymerises much less readily than its lower homologues, gave a 50% yield of 2-nitro-1-methyl-n-propyl cyanide, and 75—90% yields of nitro-tert-butyl cyanide were obtained from 1-nitro-2-methylprop-1-ene and potassium cyanide, or mixtures of potassium cyanide with hydrogen cyanide. It was shown that hydrogen cyanide alone will not add to the ethylenic linkage of this nitro-olefin, but in the presence of small quantities of potassium cyanide (5—20% of the total of CN ion) excellent yields are obtained.

Surprising results were obtained in the reduction of the 2-nitroalkyl cyanides. Catalytic

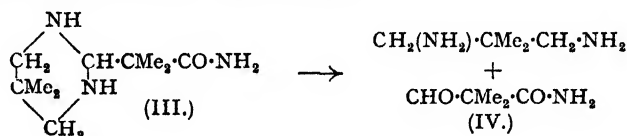
* Patent application pending.

reduction of 2-nitroisopropyl cyanide in methyl alcohol at ordinary temperature and pressure in presence of Raney nickel catalyst gave a low yield of β -aminoisobutyramide. Similar reduction of 2-nitro-1-methyl-*n*-propyl cyanide afforded a mixture of the expected aminoalkyl cyanide and β -amino- α -methylbutyramide, whilst reduction in the presence of anhydrous ammonia under pressure gave the amino-amide and some 1 : 3-diamino-2-methylpropane. In none of the above cases was the yield of reduction products good, and attention was turned for closer study to the more readily available nitro-*tert*-butyl cyanide. Chemical reduction of this with iron and hydrochloric acid gave a 65% yield of amino-*tert*-butyl cyanide and 5% of β -amino- α -dimethylpropionamide. Catalytic reduction at ordinary temperature and pressure of the nitroalkyl cyanide in methyl alcohol with a 5% palladium on calcium carbonate catalyst gave the amino-amide in 90% yield and in methyl alcoholic ammonia at 100°/100 atms. with Raney nickel, 20% of the amino-amide and 15% of 1 : 3-diamino-2 : 2-dimethylpropane were obtained. On reduction in methyl alcohol with hydrogen at ordinary temperature and pressure in the presence of Raney nickel, four products were obtained : (a) the aminoalkyl cyanide (1.5%), (b) the diamine (1.5%), (c) the amino-amide (50%), and (d) a solid, $C_{10}H_{21}ON_3$ (20%), which separated as pearly plates, m. p. 150°, when the filtered reduction solution was concentrated.

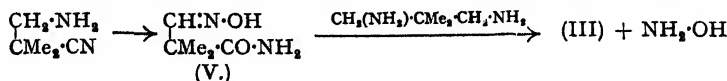
In attempting to prepare derivatives of the solid (d), it was observed that by the action of reagents for amines, the derivatives (*hydrochloride*, *picrate*, *benzoyl* derivative) which were obtained were identical with those formed directly from 1 : 3-diamino-2 : 2-dimethylpropane. It was, therefore, clear that the solid was a derivative of this diamine which was easily hydrolysed by acid and alkaline reagents, thus :



By addition of a 2*N*-hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine to the base, $C_{10}H_{21}ON_3$, in dilute hydrochloric acid, a 2 : 4-dinitrophenylhydrazone, $C_{11}H_{13}O_5N_5$, was obtained (*i.e.*, the derivative of a ketone or aldehyde, $C_5H_9O_2N$). This is formulated as α -carbamyloisobutaldehyde (IV), and the substance, $C_{10}H_{21}ON_3$, as 5 : 5-dimethyl-2-(1-carbamyloisopropyl)-hexahydropyrimidine (III); the ease of fission of substituted hexahydropyrimidines is well recognised (*cf.* Veer, *Rec. Trav. chim.*, 1938, 57, 989).



The mechanism of formation of the hexahydropyrimidine is obscure; Veer (*loc. cit.*) showed that derivatives of 1 : 3-diaminopropane condense with aldehydes merely on warming in alcoholic solution, but it is difficult to visualise conditions during a catalytic reduction which would convert the primary nitro-group, $-CH_2 \cdot NO_2$, into the aldehyde group, $-CHO$. It is considered more probable that the intermediate in this case is β -carbamyloisobutaldoxime (V), which condenses with the diaminopropane with loss of hydroxylamine, thus :



The formation of amino-amides by mild catalytic reduction of the 2-nitroalkyl cyanides is surprising. It is thought that this is not simple addition of water to the aminoalkyl cyanide; an experiment was carried out in which nitro-*tert*-butyl cyanide was shaken at room temperature in methyl alcohol with water (2 mols.) and Raney nickel (*i.e.*, the conditions of the hydrogenation). The aminoalkyl cyanide was recovered unchanged. It is possible that amide formation proceeds through an *isooxazole* as intermediate product (*isooxazoles* are known to undergo fission on hydrogenation), but no experimental proof for this can be given.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. M. ps. are uncorrected.

2-Nitroisopropyl Cyanide.—1-Nitroprop-1-ene (50 g.; this series, Part I) in alcohol (240 c.c.) was added dropwise to a well-stirred solution of potassium cyanide (40 g.) in water (300 c.c.) at -5° to 0° . The solution was stirred at 0° for a further 4 hours, acidified at $0-5^\circ$ with 5*N*-hydrochloric acid (130 c.c.), concentrated under reduced pressure at 40° to 300 c.c., and after isolation with ether the cyanide (16.4 g.; 25%), b. p. $68-70^\circ/0.5$ mm., was obtained (Found: C, 42.6; H, 5.2; N, 23.9. $C_4H_7O_2N_2$ requires C, 42.1; H, 5.3; N, 24.5%).

β -Aminoisobutyramide.—The cyanide (3.25 g.) in methyl alcohol (50 c.c.) was shaken in hydrogen

at 25°/760 mm. in the presence of Raney nickel. Absorption (1916 c.c. of hydrogen) was complete in 3½ hours. The catalyst was separated, the alcohol removed, and the product distilled, giving the amide (0.44 g.; 15%), b. p. 75–82°/0.3 mm., which was identified as the *picrate*, m. p. 232° (Found: N, 20.6. $C_8H_{10}ON_2 \cdot C_6H_5O_2N_3$ requires N, 21.1%).

2-Nitro-n-propyl Cyanide.—This compound was prepared from 2-nitroprop-1-ene (50 g.; this series, Part I) and sodium cyanide (28.2 g.) as described for the *iso*-derivative above; it was obtained as a straw-coloured liquid (10 g.; 15%), b. p. 81–82°/0.5 mm. (Found: C, 42.7; H, 5.0. $C_4H_7O_2N_2$ requires C, 42.1; H, 5.3%).

2-Nitro-1-methyl-n-propyl Cyanide.—This compound was prepared from 2-nitrobut-2-ene (58 g.; this series, Part III) in alcohol (500 c.c.) and potassium cyanide (38 g.) in water (300 c.c.) at 10–20°. Isolation in the usual way yielded the cyanide (32 g.; 50%) as a pale yellow, mobile oil, b. p. 61–65°/0.2 mm. (Found: C, 47.0; H, 6.4. $C_5H_9O_2N_2$ requires C, 46.9; H, 6.2%).

Reduction of 2-Nitro-1-methyl-n-propyl Cyanide.—(a) *With Raney nickel at ordinary pressure.* The cyanide (10.4 g.) in methyl alcohol (80 c.c.) was shaken in hydrogen at 20°/750 mm. in the presence of Raney nickel. Absorption was 4930 c.c. of hydrogen at 0°/760 mm. [Calc. (3 mols.), 5460 c.c.]. The catalyst was separated and the product distilled, giving: (i) 2-Amino-1-methyl-n-propyl cyanide, b. p. 30°/0.05 mm. (0.5 g.), characterised as its *hydrochloride*, white crystals from alcohol-ether, m. p. 156° (Found: C, 44.6; H, 8.3; N, 20.8. $C_5H_{10}N_2 \cdot HCl$ requires C, 44.6; H, 8.3; N, 20.8%). (ii) β -Amino- α -methylbutyramide, b. p. 145–155°/15 mm., 95–100°/0.05 mm. (1.7 g.), which solidified on keeping and after crystallisation from dry benzene had m. p. 62–63°. The amide was extremely deliquescent and satisfactory analyses could not be obtained. Neither the hydrochloride nor the *picrate* could be obtained in a crystalline condition, and the amide was characterised as the *picrolonate*, m. p. 214° (Found: N, 22.1. $C_5H_{10}ON_2 \cdot C_{10}H_8O_4N_4$ requires N, 22.1%).

(b) *With Raney nickel and anhydrous ammonia under pressure.* The cyanide (23 g.) in methyl alcohol (250 c.c.) and anhydrous ammonia (70 g.) was heated at 100° with hydrogen (initial pressure, 100 atms.) in an internally agitated stainless steel autoclave for 1 hour. The filtered solution was made acid to Congo-red with hydrochloric acid and evaporated to dryness at 40° under reduced pressure. The residue was treated with excess of aqueous potassium hydroxide and the product isolated with ether, giving: (i) 1:3-diamino-2-methylpropane, b. p. 60–70°/15 mm. (2 g.) (Found: equiv., 50. Calc.: 51); and (ii) β -amino- α -methylbutyramide, b. p. 145–155°/15 mm., m. p. 62–63°.

Nitro-tert-butyl Cyanide.—(a) *From 1-nitro-2-methylprop-1-ene and potassium cyanide.* 1-Nitro-2-methylprop-1-ene (101 g.; Levy and Scaife, in the press) in alcohol (500 c.c.) was added slowly to a stirred aqueous solution of potassium cyanide (65 g. in 500 c.c.) at 20–25°. Stirring was continued for 6 hours and the mixture then acidified with 5*N*-hydrochloric acid (240 c.c.) at 5–10°. The white, crystalline precipitate was collected, washed with cold water and recrystallised from ether, giving *nitro-tert-butyl cyanide* (96 g.; 75%), m. p. 42°, b. p. 66–67°/0.2 mm. (Found: C, 47.1; H, 6.1; N, 21.3. $C_5H_9O_2N_2$ requires C, 46.9; H, 6.2; N, 21.9%).

(b) *From 1-nitro-2-methylprop-1-ene, hydrogen cyanide, and potassium cyanide.* A mixture of the nitro-olefin (10.1 g.), hydrogen cyanide (6 g.), and potassium cyanide (0.325 g.; 5%) in 50% aqueous alcohol (50 c.c.) was stirred at room temperature for 24 hours. Water (50 c.c.) was then added and the solution at 0–5° made acid to Congo-red with hydrochloric acid. The precipitated cyanide was isolated with ether and recrystallised from ether, m. p. 42°. Yield, 10.3 g. (83%). In this preparation, the use of 1% of potassium cyanide reduced the yield to 10%; with 20% of potassium cyanide the yield was 87%; in the absence of potassium cyanide (hydrogen cyanide alone) no nitroalkyl cyanide was obtained.

(c) *From nitro-tert-butyl acetate and potassium cyanide.* Nitro-tert-butyl acetate (8 g.; this series, Part XVIII) was added dropwise to a vigorously stirred aqueous solution of potassium cyanide (4 g. in 25 c.c.) at 25–30°. Stirring was continued for 16 hours at 30°, the solution acidified at 0–5° with 5*N*-hydrochloric acid, and the precipitated cyanide crystallised from ether, m. p. 42°. Yield, 2.5 g. (40%).

Reduction of Nitro-tert-butyl Cyanide.—(a) *With iron and hydrochloric acid.* A mixture of iron filings (35 g.), concentrated hydrochloric acid (10 c.c.), and water (75 c.c.) was allowed to react at 60–70° until evolution of hydrogen ceased. The cyanide (21 g.) in alcohol (50 c.c.) was then added at a rate sufficient to maintain the temperature of the vigorously stirred mixture at 60–70°, and stirring was continued at the same temperature for a further 8 hours. The mixture was filtered, acidified with concentrated hydrochloric acid, and evaporated to dryness, and the free bases, liberated by addition of an excess of 50% aqueous potassium hydroxide, were isolated with ether. Distillation gave: (i) *Amino-tert-butyl cyanide* (10.2 g.; 65%), b. p. 63°/15 mm., m. p. 10° (Found: C, 61.5; H, 9.7. $C_5H_{11}N_2$ requires C, 61.2; H, 10.2%); *hydrochloride*, from alcohol, m. p. 260° (Found: C, 44.5; H, 8.2; N, 20.6. $C_5H_{10}N_2 \cdot HCl$ requires C, 44.6; H, 8.2; N, 20.8%); *picrate*, from water, m. p. 183° (Found: C, 40.3; H, 3.8; N, 21.4. $C_5H_{10}N_2 \cdot C_6H_5O_2N_3$ requires C, 40.4; H, 3.9; N, 21.4%); *benzoyl derivative*, from alcohol, m. p. 122° (Found: C, 71.3; H, 6.6; N, 13.9. $C_{11}H_{14}ON_2$ requires C, 71.3; H, 6.6; N, 13.9%). Reduction of this aminoalkyl cyanide by shaking in methyl-alcoholic solution with hydrogen and Raney nickel at ordinary temperature and pressure afforded 1:3-diamino-2:2-dimethylpropane, b. p. 65°/15 mm., 153°/760 mm. (Found: C, 58.4; H, 13.6; N, 27.0. $C_6H_{14}N_2$ requires C, 58.8; H, 13.7; N, 27.4%); dihydrochloride, m. p. 259° [Komppa and Seron (*Ann. Acad. Sci. Fennica*, 1933, 374, No. 7, 8; cf. *Chem. Abs.*, 1933, 3964) give m. p. 280–281°] (Found: C, 34.5; H, 8.6; N, 15.7; Cl, 40.1. Calc. for $C_6H_{14}N_2 \cdot 2HCl$: C, 34.3; H, 9.1; N, 16.0; Cl, 40.6%); dipicrate, m. p. 234° (Komppa and Seron, *loc. cit.*, give m. p. 240°) (Found: C, 36.6; H, 3.6; N, 19.8. Calc. for $C_6H_{14}N_2 \cdot 2C_6H_5O_2N_3$: C, 36.4; H, 3.6; N, 20.0%); *dibenzoyl derivative*, long needles from aqueous alcohol, m. p. 152° (Found: C, 73.7; H, 7.3; N, 9.0. $C_{18}H_{22}O_4N_4$ requires C, 73.5; H, 7.1; N, 9.0%). (ii) β -Amino- α -dimethylpropionamide (1 g.; 5%), b. p. 145°/15 mm., which solidified and after crystallisation from dry benzene had m. p. 74–75° (Found: equiv. by titration, 115. Calc.: 116). This compound was highly deliquescent and satisfactory analyses could not be obtained; it was characterised as the following derivatives: *hydrochloride*, fine needles from absolute alcohol, m. p. 172° (Found: C, 39.6; H, 8.7;

N, 17.8; Cl, 23.3. $C_8H_{11}ON_2.HCl$ requires C, 39.5; H, 8.5; N, 18.3; Cl, 23.3%; *hydrobromide*, plates from absolute alcohol, m. p. 202° (Found: C, 30.5; H, 6.2; N, 14.1; Br, 40.8. $C_8H_{11}ON_2.HBr$ requires C, 30.5; H, 6.6; N, 14.2; Br, 40.6%); *picrate*, flat prisms from alcohol, m. p. 190° (Found: C, 38.4; H, 4.2; N, 20.4. $C_8H_{11}ON_2.C_6H_3O_7N_3$ requires C, 38.3; H, 4.3; N, 20.3%); *phenylurea*, prisms from alcohol, m. p. $199-200^\circ$ (Found: C, 61.2; H, 7.0; N, 17.2. $C_{11}H_{17}O_2N_2$ requires C, 61.2; H, 7.2; N, 17.8%). The *benzoyl* derivative, prisms from alcohol-ether, m. p. 151° (Found: C, 65.5; H, 7.2; N, 12.6. $C_{12}H_{15}O_2N_2$ requires C, 65.4; H, 7.3; N, 12.7%), on being heated with excess of thionyl chloride, gave 2-benzamido-1:1-dimethyl-*tert*-butyl cyanide, m. p. 122° , identical with that described above.

(b) *Reduction with hydrogen and Raney nickel at ordinary pressure.* The nitroalkyl cyanide (42 g.) in methyl alcohol (450 c.c.) was shaken in hydrogen in presence of Raney nickel at ordinary pressure and temperature. Absorption was 22.7 l. of hydrogen at N.T.P. [Calc. (3 mols.), 22.4 l.]. The catalyst was separated and the filtrate concentrated, giving a solid (A) and a liquid, separated by filtration. The liquid was distilled, giving the following: (i) Amino-*tert*-butyl cyanide (0.5 g.; 1.5%), m. p. 10° . (ii) 1:3-Diamino-2:2-dimethylpropane (0.5 g.; 1.5%); dihydrochloride, m. p. 259° ; dipicrate, m. p. 234° . (iii) β -Amino- $\alpha\alpha$ -dimethylpropionamide (19 g.; 50%), m. p. $74-75^\circ$. The solid (A), above, recrystallised from absolute alcohol, gave 5:5-dimethyl-2-(1-carbamylisopropyl)hexahydropyrimidine (6.5 g.; 20%) in pearly plates, m. p. 150° (Found: C, 60.2; H, 10.1; N, 20.6. $C_{10}H_{15}ON_2$ requires C, 60.3; H, 10.5; N, 21.0%). On addition of a dry, ethereal solution of hydrogen chloride to the base in alcohol at $0-10^\circ$, 1:3-diamino-2:2-dimethylpropane dihydrochloride, m. p. and mixed m. p. with an authentic specimen 259° , separated in 42% yield. Similarly, addition of hot, aqueous picric acid to an alcoholic solution of the hydropyrimidine gave 1:3-diamino-2:2-dimethylpropane dipicrate, m. p. and mixed m. p. 234° , and benzooylation by the Schotten-Baumann procedure gave 1:3-dibenzamido-2:2-dimethylpropane, m. p. and mixed m. p. 152° . Addition of 2:4-dinitrophenylhydrazine in 2N-hydrochloric acid to a solution of the pyrimidine in hydrochloric acid gave a pale yellow, crystalline precipitate, which, crystallised from methyl alcohol, yielded β -carbamylisobutaldehyde 2:4-dinitrophenylhydrazone, m. p. 196° (Found: C, 44.7; H, 4.4; N, 23.6. $C_{11}H_{13}O_5N_5$ requires C, 44.7; H, 4.4; N, 23.7%).

(c) *Reduction with hydrogen and palladium.* The nitro-cyanide (10 g.) in methyl alcohol (50 c.c.) was shaken in hydrogen with a 5% palladium on calcium carbonate catalyst at ordinary pressure. Absorption was 5.2 l. of hydrogen at N.T.P. [Calc. (3 mols.), 5.25 l.]. The catalyst was removed and the solution distilled, yielding β -amino- $\alpha\alpha$ -dimethylpropionamide, m. p. $74-75^\circ$ (8.0 g.; 89%).

(d) *Reduction with hydrogen and Raney nickel in presence of anhydrous ammonia.* The nitro-cyanide (45 g.) in methyl alcohol (250 c.c.) and anhydrous ammonia (140 g.) was heated at 100° in an internally agitated, stainless steel autoclave with hydrogen at 100 atms. initial pressure and Raney nickel (10 g.). Hydrogenation was complete in 1 hour. After evaporation of the ammonia, the catalyst was removed and the product distilled, giving: (i) 1:3-Diamino-2:2-dimethylpropane, b. p. $65^\circ/15$ mm. (5.5 g.; 15%). (ii) β -Amino- $\alpha\alpha$ -dimethylpropionamide, m. p. $74-76^\circ$ (8.2 g.; 20%).

β -Amino- $\alpha\alpha$ -dimethylpropionic Acid.— β -Amino- $\alpha\alpha$ -dimethylpropionamide (9.2 g.) was refluxed for 4 hours with 40% sulphuric acid (90 c.c.). The solution was diluted with water (300 c.c.) and barium carbonate (slight excess calculated on the sulphuric acid) was added slowly to the boiling solution through which a current of steam was passed to remove the ammonia. The excess of barium carbonate was decomposed by neutralisation (to Congo-red) with 2N-sulphuric acid, and the barium sulphate removed by filtration. The filtrate was concentrated to 75 c.c., and traces of sulphuric acid were precipitated with lead carbonate, the lead sulphate was filtered off, and the filtrate saturated with hydrogen sulphide. After removal of lead sulphide, the filtrate was concentrated and yielded β -amino- $\alpha\alpha$ -dimethylpropionic acid, which separated from aqueous alcohol as large hexagonal prisms, m. p. 246° (decomp.) in 82% yield (Kohn and Schmidt, *Monatsh.*, 1907, 28, 1056, give decomp. ca. 220°) (Found: C, 51.1; H, 9.4; N, 12.3. Calc. for $C_8H_{11}O_2N$: C, 51.3; H, 9.4; N, 12.0%).

Methyl β -Amino- $\alpha\alpha$ -dimethylpropionate.—The acid was esterified in methyl alcohol with dry hydrogen chloride in the usual way; evaporation of the methyl alcohol yielded the *methyl ester hydrochloride*, m. p. 164° (80% yield) (Found: C, 43.0; H, 8.2; N, 8.2. $C_8H_{13}O_2N.HCl$ requires C, 43.0; H, 8.4; N, 8.4%). Addition of 10N-sodium hydroxide to an aqueous solution of the hydrochloride, followed by isolation with ether and distillation, afforded the *methyl ester*, b. p. $57^\circ/11$ mm., which separated from dry ether as highly deliquescent prisms, m. p. 64° (Found: C, 54.8; H, 9.9; N, 10.5. $C_8H_{13}O_2N$ requires C, 55.0; H, 9.9; N, 10.7%). The ester was completely unchanged after standing for 2 days at 0° with methyl alcoholic ammonia; with concentrated aqueous ammonia, at 60° for 3 days, hydrolysis to the acid occurred. The *ethyl ester hydrochloride*, similarly formed, had m. p. 91° (Found: C, 45.6; H, 8.4; N, 7.8; Cl, 19.7. $C_7H_{13}O_2N.HCl$ requires C, 46.2; H, 8.8; N, 7.7; Cl, 19.7%).

β -Benzamido- $\alpha\alpha$ -dimethylpropionic acid, m. p. 151° (Kohn and Schmidt, *loc. cit.*, give m. p. $149-151^\circ$) (3 g.) was treated with freshly distilled thionyl chloride (6.5 c.c.; 6 mols.) and the reaction completed by 1 hour's boiling under reflux. The excess of thionyl chloride was removed under reduced pressure at $70-80^\circ$, and to the residual, pale yellow oil, saturated methyl-alcoholic ammonia (25 c.c.) was added at 0° . The solution was evaporated, the residual solid triturated with water to remove ammonium chloride, and the residue, crystallised from aqueous alcohol, gave a small yield of *benzamido-tert*-butyl cyanide identical with that described above, m. p. and mixed m. p. 122° . Repetition of this experiment with only one mol. of thionyl chloride in benzene, and treatment of the crude acid chloride with aqueous (d 0.88) ammonia, gave 90% of β -benzamido- $\alpha\alpha$ -dimethylpropionamide, m. p. 151° , identical with the benzoyl derivative of the amino-amide (see above).

The authors wish to acknowledge the interest and advice of Dr. H. A. Piggott in this work.

292. Aliphatic Nitro-compounds. Part XIII. Preparation of 3-Nitro-1-arylalkyl Cyanides by Interaction of Arylmethyl Cyanides and α -Nitro-olefins.*

By G. D. BUCKLEY, F. G. HUNT, and A. LOWE.

Arylmethyl cyanides, but not 1-arylethyl cyanides, react with α -nitro-olefins in presence of alkali alkoxides (preferably potassium *tert.*-amyloxyde) to give 3-nitro-1-arylalkyl cyanides. 2-Nitroalkyl esters may be used in place of nitro-olefins, e.g., 1-nitro-2-methylprop-1-ene or nitro*tert.*-butyl nitrate reacts with benzyl cyanide to give 3-nitro-1-phenyl-2:2-dimethylpropyl cyanide (II).

THE use of α -nitro-olefins as the unsaturated component in reactions of the Michael type has been described in earlier parts in this series and elsewhere. Active methylene compounds which have been used successfully in such reactions include primary and secondary nitro-paraffins (Part VIII), ethyl malonate (Kohler *et al.*, *J. Amer. Chem. Soc.*, 1919, **41**, 764; 1926, **48**, 1770), and acetone (Hass and Riley, *Chem. Reviews*, 1943, **32**, 373), and this type of reaction has now been extended to the preparation of 3-nitro-1-arylalkyl cyanides by addition of arylmethyl cyanides to α -nitro-olefins.



Benzyl cyanide reacted readily with 1-nitro-2-methylprop-1-ene in the presence of sodium methoxide to give 3-nitro-1-phenyl-2:2-dimethylpropyl cyanide (II) in 12% yield, but by using potassium *tert.*-amyloxyde in place of the methoxide catalyst the yield was raised to 60%. From *p*-bromobenzyl cyanide and 1-naphthylmethyl cyanide, with the amyloxyde catalyst, 3-nitro-1-*p*-bromophenyl-2:2-dimethylpropyl cyanide (III) and 3-nitro-1-(1-naphthyl)-2:2-dimethylpropyl cyanide (IV) were obtained in 48% and 70% yield respectively.

The adducts to 2-nitrobut-2-ene and 1-nitrocyclohexene were obtained as viscous oils from which it was difficult to isolate the pure diastereoisomerides: thus, benzyl cyanide with 2-nitrobut-2-ene gave 3-nitro-1-phenyl-2-methyl-*n*-butyl cyanide (I) and *p*-bromobenzyl cyanide added to 1-nitrocyclohexene to form 2-nitro-1-(*p*-bromo- α -cyanobenzyl)cyclohexane (V) from which a crystalline isomer was isolated in small yield and with considerable difficulty. An attempt to add 1-phenylethyl cyanide (Meyer, *Annalen*, 1899, **250**, 123) to 1-nitro-2-methylprop-1-ene in the presence of potassium *tert.*-amyloxyde failed.



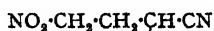
(I.)



(II.)



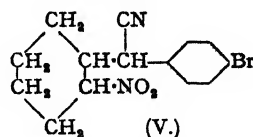
(VI.)



(III.)



(IV.)



(V.)

Esters of 2-nitro-alcohols yield nitro-olefins on treatment with alkalis, and it has been shown that such esters can be used instead of nitro-olefins in addition reactions provided that sufficient alkali is present to neutralise the liberated acid. Nitro-*tert.*-butyl nitrate reacted with 2 mols. of the potassium salt of benzyl cyanide to give 3-nitro-1-phenyl-2:2-dimethylpropyl cyanide identical with the product obtained from 1-nitro-2-methylprop-1-ene, and under similar conditions 2-nitroisopropyl acetate gave 3-nitro-1-phenyl-2-methylpropyl cyanide (VI).

The reaction is of fairly general application for the preparation of 3-nitro-1-arylalkyl cyanides and is complementary to the method of preparation described in Part XIV of this series. The two methods in conjunction make possible the preparation of a wide variety of these hitherto inaccessible compounds.

EXPERIMENTAL.

Microanalyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

3-Nitro-1-phenyl-2-methyl-*n*-butyl Cyanide (I).—Benzyl cyanide (60 g.) was run into a solution of sodium methoxide [from sodium (12 g.) in methyl alcohol (200 c.c.)] at 20° and a solution of 2-nitrobut-2-ene (50 g.; this series, Part III) in methyl alcohol (100 c.c.) added dropwise during 1 hour at 5–10°. The mixture was heated at 60° for 18 hours, poured into water, and extracted with ether. The extract was washed with water and discarded, and the combined aqueous solutions were acidified

* Patent application pending.

with acetic acid (50 c.c.) and extracted with ether. The extract was dried and fractionated, giving the cyanide as a yellow oil (28.5 g.), b. p. 129—134°/0.2 mm. (Found: N, 13.15. $C_{11}H_{14}O_2N_2$ requires N, 12.85%).

3-Nitro-1-phenyl-2:2-dimethylpropyl Cyanide (II).—(a) From 1-nitro-2-methylprop-1-ene. To a stirred, ice-cooled solution of potassium *tert*-amyloxyde (from 8 g. of potassium), benzyl cyanide (23.5 g.) was added at 5—10°. 1-Nitro-2-methylprop-1-ene (20 g.; Levy and Scaife, in the press) was then added dropwise during 1 hour at 5—10°, and the reaction was completed by stirring at 60° for 2 hours. After cooling, the mixture was diluted with water and extracted with ether. The ethereal extract was washed with water and discarded, and the combined aqueous solutions were acidified with acetic acid (13 c.c.) and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, evaporated, and the residue (25 g.; 60% yield), consisting of almost pure 3-nitro-1-phenyl-2:2-dimethylpropyl cyanide, was left in a desiccator until completely solid. Crystallisation from a little methyl alcohol gave colourless needles, m. p. 59° (Found: C, 66.15; H, 5.95; N, 12.9. $C_{12}H_{14}O_2N_2$ requires C, 66.05; H, 6.4; N, 12.85%).

(b) From nitro-*tert*-butyl nitrate. A solution of potassium *tert*-amyloxyde [from potassium (2 g.) in *tert*-amyl alcohol (40 c.c.)] was treated with benzyl cyanide (5.85 g.) as before. Nitro-*tert*-butyl nitrate (4.1 g.; Levy and Scaife, in the press) in *tert*-amyl alcohol (5 c.c.) was added during 1 hour at 5—10°, and the mixture was then stirred at 60° for 2 hours and worked up as before. The product, m. p. 59°, was identical with that prepared above from 1-nitro-2-methylprop-1-ene.

3-Nitro-1-p-bromophenyl-2:2-dimethylpropyl Cyanide (III).—*p*-Bromobenzyl cyanide (9.8 g.) was brought into reaction with 1-nitro-2-methylprop-1-ene (5.05 g.) as described for benzyl cyanide. After several days in a desiccator the product solidified (7.1 g.; 48% yield), and crystallisation from methyl alcohol gave colourless needles of 3-nitro-1-p-bromophenyl-2:2-dimethylpropyl cyanide, m. p. 72—74° (Found: N, 9.4; Br, 27.55. $C_{11}H_{11}O_2N_2Br$ requires N, 9.4; Br, 26.9%).

3-Nitro-1-(1-naphthyl)-2:2-dimethylpropyl Cyanide (IV).—1-Naphthylmethyl cyanide (5 g.) was brought into reaction with 1-nitro-2-methylprop-1-ene (3 g.) as described for benzyl cyanide. The product (5.5 g.; 70% yield), isolated as before, solidified on removal of the ether. After two recrystallisations from alcohol (charcoal) the cyanide was obtained as long, colourless needles, m. p. 116° (Found: C, 71.7; H, 6.0; N, 10.4. $C_{16}H_{15}O_2N_2$ requires C, 71.65; H, 6.0; N, 10.4%).

3-Nitro-1-phenyl-2-methylpropyl Cyanide (VI).—A solution of potassium *tert*-amyloxyde [from potassium (8 g.) in *tert*-amyl alcohol (160 c.c.)] was treated with benzyl cyanide (23.5 g.) as before. 2-Nitroisopropyl acetate (14.6 g.; Schmidt and Rutz, *Ber.*, 1928, **61**, 2142) was then added during 1 hour at 5—10°, and the resulting solution was stirred at 60° for 2 hours, cooled to 20°, and diluted with water. Isolation in the usual way yielded 3-nitro-1-phenyl-2-methylpropyl cyanide as a pale yellow oil (6.7 g.; 25% yield), b. p. 122—126°/0.15 mm. (Found: C, 65.3; H, 5.55; N, 14.2. $C_{11}H_{13}O_2N_2$ requires C, 64.7; H, 5.9; N, 13.75%).

2-Nitro-1-(p-bromo- α -cyanobenzyl)cyclohexane (V).—1-Nitrocyclohexene (14 g.; Wieland *et al.*, *Annalen*, 1921, **424**, 71) was brought into reaction with *p*-bromobenzyl cyanide (21.6 g.) in presence of potassium *tert*-amyloxyde as previously described. The crude product, isolated as before, was a viscous oil (10.7 g.), apparently a mixture of diastereoisomers. After several days in a desiccator, it partly crystallised, and was then treated with a little alcohol and the crystals were collected (2.9 g.). Recrystallisation from methyl alcohol gave the compound as colourless granules, m. p. 103—104° (Found: N, 8.75; Br, 25.2. $C_{14}H_{15}O_2N_2Br$ requires N, 8.65; Br, 24.75%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES,

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[Received, January 23rd, 1947.]

293. Aliphatic Nitro-compounds. Part XIV. Preparation of 3-Nitroalkyl Cyanides by Reaction of Nitro-paraffins with Unsaturated Cyanides.*

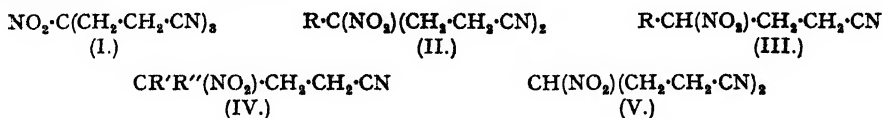
By G. D. BUCKLEY, T. J. ELLIOTT, F. G. HUNT, and A. LOWE.

A series of 3-nitroalkyl cyanides is prepared by the interaction of vinyl cyanide with primary and secondary nitro-paraffins in the presence of alkali. Both propenyl and allyl cyanide react with 1-nitropropane to give 3-nitro-2-methyl-n-amyl cyanide and with 2-nitropropane to give 3-nitro-2:3-dimethyl-n-butyl cyanide. α -Cyanostilbenes react with primary nitro-compounds in presence of secondary aliphatic amines to give 3-nitro-1:2-diaryllalkyl cyanides, e.g., α -cyanostilbene and nitromethane give 3-nitro-1:2-diphenylpropyl cyanide (VIII; R = H).

WHEN this work was carried out only two 3-nitroalkyl cyanides had been reported: 3-nitropropyl cyanide, prepared by Henry (*Bull. Acad. Sci. Belg.*, 1895, **36**, 152) by the action of silver nitrite on 3-iodopropyl cyanide, and nitrotris-(2-cyanoethyl)methane (I) prepared by Bruson and Reiner (*J. Amer. Chem. Soc.*, 1943, **65**, 23) by addition of nitromethane to vinyl cyanide (acrylonitrile). As large quantities of 3-nitroalkyl cyanides were required in connection with other investigations, we decided to extend the application of Bruson's method to other olefins and nitro-paraffins.

* Patent application pending.

Since our work was completed, Bruson (U.S.P. 2,361,259) has reported the addition of nitro-paraffins to vinyl cyanide in an inert solvent (e.g., dioxan or *tert.*-butyl alcohol), preferably at about 40° and in the presence of a small amount of alkali such as sodium hydroxide or a quaternary ammonium base as catalyst. In this way nitromethane gave the tris-adduct (I), other primary nitro-paraffins gave mixtures of bis- (II) and mono-adducts (III), whereas secondary nitro-paraffins gave mono-adducts (IV).

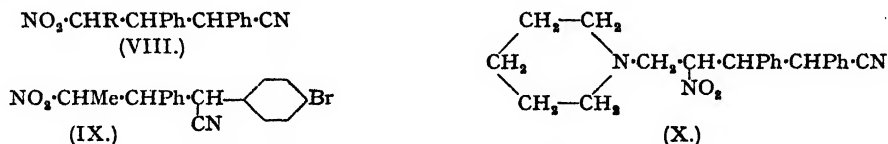


We have found it more convenient to effect the addition by refluxing an alcoholic solution of the cyanide, nitro-paraffin, and catalyst for a short time. The yields of mono-adducts (type III) from primary nitro-paraffins are improved by using a full molecular proportion of alkali as condensing agent, and with this technique, the bis-adduct to nitromethane (V) has been obtained.

The following new 4-nitro-cyanides have been made by this method: 1-nitro-1-(2-cyanoethyl)-cyclohexane, 3-nitro-4-methoxy-4-phenyl-3-methyl-*n*-butyl cyanide (VI), 3-nitro-5-*n*-butylsulphonyl-3-methyl-*n*-amyl cyanide, and 3-nitro-1:5-dicyanopentane. The known 3-nitro-3-methyl-*n*-butyl cyanide and 3-nitro-*n*-butyl cyanide (cf. Bruson, *loc. cit.*) have been prepared by the modified method: the first of these has been converted into its iminoethyl ether and amidine hydrochloride, and the second has been hydrolysed with acid to 3-keto-*n*-butyl cyanide (lævulonitrile).

The general method of addition has been extended by the use of substituted vinyl cyanides. Thus 2-nitropropane reacted with isopropenyl cyanide (methacrylonitrile) in presence of a little methyltriethylammonium hydroxide to give 3-nitro-1:3-dimethyl-*n*-butyl cyanide and with propenyl cyanide (crotononitrile) to give the isomeric 3-nitro-2:3-dimethyl-*n*-butyl cyanide, which was also formed by interaction of allyl cyanide and 2-nitropropane. Similarly, both propenyl and allyl cyanide reacted with 1-nitropropane to give 3-nitro-2-methyl-*n*-amyl cyanide (VII), the identity of the products being established by hydrolysis to 3-keto-2-methyl-*n*-amyl cyanide, which was characterised as the 2:4-dinitrophenylhydrazone. The allyl cyanide was presumably isomerised to propenyl cyanide by the alkaline catalyst before reaction with the nitro-paraffin, but a curious feature was that in both cases much higher yields of nitro-cyanide were obtained from allyl cyanide than from propenyl cyanide.

Aryl substituted vinyl cyanides behaved in an anomalous manner. Attempts to cause nitroethane to react with α -cyanostilbene in presence of strong alkalis failed, but by using a secondary aliphatic amine as catalyst 3-nitro-1:2-diphenyl-*n*-butyl cyanide (VIII; R = Me) was produced in 60% yield.



Similarly, nitromethane gave one of the isomerides of 3-nitro-1:2-diphenyl-*n*-propyl cyanide (VIII; R = H), and nitroethane reacted with 4-bromo- α -cyanostilbene to give one of the isomerides of 3-nitro-2-phenyl-1-*p*-bromophenyl-*n*-butyl cyanide (IX), but all attempts to cause secondary nitro-paraffins to react with α -cyanostilbene were unsuccessful. Methyl 2-nitroethyl ether reacted with α -cyanostilbene in the presence of piperidine, but unexpectedly the product was acid-soluble, the methoxyl group having been replaced by a piperidine residue to give 3-nitro-4-piperidino-1:2-diphenyl-*n*-butyl cyanide (X).

In many of the above products (IV), (VII), (VIII), (IX), and (X) there is more than one asymmetric carbon atom, so that the compounds would be expected to be formed as mixtures of stereoisomerides. In these cases, only one isomer has been identified and no attempt has been made to isolate the other stereoisomerides: the yields recorded therefore do not necessarily indicate the extent of the reaction.

EXPERIMENTAL.

Microanalyses are by Mr. E. S. Morton. M. ps. are uncorrected.

3-Nitro-3-methyl-*n*-butyl Cyanide.—Aqueous potassium hydroxide (10 c.c. of 33%) was added to a solution of 2-nitropropane (261 g.) in alcohol (750 c.c.), which was then heated to boiling. Vinyl cyanide

(159 g.) was run into the stirred solution at such a rate that the mixture refluxed gently. After a further 1 hour's refluxing, the solution was cooled, made just acid to Congo-red by addition of 20% sulphuric acid, stirred with barium carbonate to remove excess of acid, and filtered. The filtered solution was fractionated to give the cyanide as a colourless oil (330 g.), b. p. 70°/0.09 mm. (Bruson, *loc. cit.*, gives b. p. 105—107°/1 mm.). (Found: C, 50.55; H, 7.0; N, 19.7. Calc. for $C_8H_{10}O_2N_2$: C, 50.7; H, 7.05; N, 19.7%). The iminoethyl ether hydrochloride, prepared by passing dry hydrogen chloride into an alcoholic solution of the cyanide below 20°, had m. p. 108° (Found: N, 11.75; Cl, 16.2. $C_8H_{10}O_2N_2 \cdot HCl$ requires N, 12.4; Cl, 15.8%). The amidine hydrochloride, prepared by the action of alcoholic ammonia on the iminoethyl ether hydrochloride, had m. p. 214° (Found: Cl, 18.4. $C_8H_{10}O_2N_3 \cdot HCl$ requires Cl, 18.15%).

1-Nitro-1-(2-cyanoethyl)cyclohexane.—Nitrocyclohexane (43 g.) was brought into reaction with vinyl cyanide (18 g.) as described for 2-nitropropane. Distillation gave the product as a pale yellow oil (24 g.), b. p. 98—108°/0.15 mm., which from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 42° (Found: C, 59.9; H, 7.45; N, 15.25. $C_8H_{14}O_2N_2$ requires C, 59.35; H, 7.7; N, 15.4%).

3-Nitro-1:2-dimethyl-n-butyl Cyanide.—(a) 2-Nitropropane (6.65 g.), allyl cyanide (5.0 g.), ethyl alcohol (50 c.c.), and aqueous methyltriethylammonium hydroxide (2.7 c.c. of 37%) were refluxed for 20 hours. The product (9.45 g.; 80%), isolated as in the previous cases, was a colourless oil, b. p. 86—87°/0.24 mm. (Found: C, 54.5; H, 7.8; N, 17.55. $C_7H_{12}O_2N_2$ requires C, 53.85; H, 7.7; N, 17.95%).

(b) The above experiment was repeated using propenyl cyanide in place of allyl cyanide. A colourless oil, b. p. 86—87°/0.24 mm., was isolated in 55% yield (Found: N, 18.25%).

3-Nitro-1:2-dimethyl-n-butyl Cyanide.—2-Nitropropane (8.9 g.) was brought into reaction with isopropenyl cyanide (7.0 g.) as described above for propenyl cyanide. After isolation as before, the crude product was distilled, giving the cyanide (6.3 g.), b. p. 65°/0.08 mm., m. p. 51—53° (from alcohol) (Found: C, 53.5; H, 7.35; N, 17.7. $C_7H_{12}O_2N_2$ requires C, 53.85; H, 7.7; N, 17.95%).

3-Nitro-4-methoxy-4-phenyl-3-methyl-n-butyl Cyanide.—Aqueous sodium hydroxide (5 c.c. of 32%) and vinyl cyanide (37.5 g.) were added to a solution of methyl 2-nitro-1-phenylpropyl ether (48.5 g.; this series, Part III) in dioxan (100 c.c.), and the mixture was stirred at 20° for 18 hours. The solution was poured into water, acidified with hydrochloric acid, and extracted with chloroform. Fractionation of the extract gave the product as a colourless oil (50 g.), b. p. 163—167°/0.5 mm. (Found: C, 62.5; H, 6.3; N, 11.3. $C_{13}H_{16}O_3N_2$ requires C, 62.9; H, 6.45; N, 11.3%).

3-Nitro-5-n-butylsulphonyl-3-methyl-n-amyl Cyanide.—Vinyl cyanide (1.05 g.) and methyltriethylammonium hydroxide (0.75 c.c. of 37%) were added to a solution of 3-nitrodibutyl sulphone (4.2 g.; this series, Part XVII) in alcohol (20 c.c.), which was then refluxed for 3 hours, cooled, and poured into water (250 c.c.). The mixture was extracted with ether and the extract was washed with dilute aqueous sodium hydroxide, dried, and the solvent removed to yield the cyanide as a very viscous brown oil, which could not be distilled or induced to crystallise (Found: N, 9.9; S, 11.4. $C_{11}H_{20}O_4N_2S$ requires N, 10.5; S, 11.6%).

4-Nitro-n-butyl Cyanide.—A solution of sodium methoxide [from sodium (11.5 g.) and methyl alcohol (150 c.c.)] was slowly run into a stirred solution of nitroethane (38 g.) in methyl alcohol (75 c.c.) at 0—10°. Vinyl cyanide (27 g.) was slowly added at 20—25°; during the addition the white precipitate of the sodium salt of nitroethane dissolved. The mixture was then acidified with acetic acid (32 g.), the solvent removed under reduced pressure at 40°, and the residue diluted with sufficient water to dissolve the sodium acetate and extracted with ether. The extract was dried and fractionated to give the cyanide as a colourless oil (19 g.), b. p. 82—84°/0.25 mm. (Bruson, *loc. cit.*, gives b. p. 107—110°/2 mm.) (Found: N, 21.65. Calc. for $C_5H_9O_2N_2$: N, 21.85%).

3-Keto-n-butyl Cyanide.—3-Nitro-n-butyl cyanide (13 g.) was dissolved in alcohol (10 c.c.) and aqueous sodium hydroxide (8 c.c. of 32%) was added at 10—15°. The resulting solution was diluted with water (30 c.c.) and run into dilute sulphuric acid (70 c.c. of 30%) at 10—15°. After being stirred for a further 15 minutes the mixture was extracted with ether. The extract was dried and fractionated to give the ketone as a colourless oil, b. p. 98—102°/9 mm. The 2:4-dinitrophenylhydrazones formed orange leaflets, m. p. 146°, from 2-ethoxyethyl alcohol (Found: C, 47.55; H, 4.05; N, 25.25. $C_{11}H_{11}O_4N_2$ requires C, 47.65; H, 4.0; N, 25.25%).

3-Nitro-2-methyl-n-amyl Cyanide.—(a) 1-Nitropropane (8.9 g.) was added dropwise to a solution of potassium hydroxide (5.6 g.) in alcohol (20 c.c.), the temperature being kept below 10°. The solution was then stirred at 50° and a solution of allyl cyanide (6.7 g.) in alcohol (30 c.c.) was added dropwise. The solution was stirred at 50° for 18 hours, cooled, and neutralised by dropwise addition of 5N-sulphuric acid, followed by treatment with barium carbonate. The filtered solution was fractionated, giving 3-nitro-2-methyl-n-amyl cyanide as a colourless oil (12.5 g.; 80% yield), b. p. 76°/0.1 mm.

The oil (1 g.), dissolved in a solution of sodium hydroxide (0.5 g.) in alcohol (5 c.c.) and water (5 c.c.), was added dropwise to ice-cold sulphuric acid (10 c.c. of 30%) and the mixture poured into excess of a saturated solution of 2:4-dinitrophenylhydrazine in 2N-hydrochloric acid. After standing overnight the precipitate was collected and crystallised from alcohol, giving 3-keto-2-methyl-n-amyl cyanide 2:4-dinitrophenylhydrazone as orange needles, m. p. 103—104° (Found: C, 51.25; H, 4.7; N, 23.25. $C_{13}H_{15}O_4N_4$ requires C, 51.15; H, 4.9; N, 22.95%).

(b) The above experiment was repeated using propenyl cyanide in place of allyl cyanide. This gave the nitro-cyanide in 35% yield as a colourless oil, b. p. 74—75°/0.09 mm. Hydrolysis and reaction with 2:4-dinitrophenylhydrazine as before gave a product, m. p. 102—103°, identical with the 2:4-dinitrophenylhydrazone described in (a) above (Found: N, 22.95%).

3-Nitro-1:5-dicyanopentane.—A solution of sodium methoxide [from sodium (7.5 g.) and methyl alcohol (150 c.c.)] was added dropwise to a stirred solution of nitromethane (20 g.) in methyl alcohol (75 c.c.) at 0—10°, and vinyl cyanide (32 g.) added during 1 hour. The mixture was treated with acetic acid (20 g.), concentrated under reduced pressure, and the residue diluted with water (300 c.c.) and shaken with ether, which caused the separation of crystals. Repeated recrystallisation from alcohol (charcoal) gave colourless needles (4 g.) of 3-nitro-1:5-dicyanopentane, m. p. 63° (Found: C, 50.2; H, 5.4; N, 24.95. $C_5H_6O_2N_3$ requires C, 50.3; H, 5.4; N, 25.1%).

3-Nitro-1 : 5-dicyano-3-p-bromophenylpentane.—Methyltriethylammonium hydroxide (1 c.c. of 37%) was added to a solution of *p*-bromophenylnitromethane (4.3 g.) and vinyl cyanide (1.6 g.) in *tert*-butyl alcohol (50 c.c.). Next day, the precipitate was collected (1.7 g.) and recrystallised repeatedly from alcohol, giving the dicyanide as colourless needles, m. p. 138—139° (Found : N, 13.2; Br, 24.45. Calc. for $C_{12}H_{10}O_2N_4Br$: N, 13.05; Br, 24.85%).

3-Nitro-1 : 2-diphenyl-*n*-butyl Cyanide (III; R = Me).— α -Cyanostilbene (205 g.), nitroethane (75 g.), and diethylamine (100 c.c.) were heated at 35—40° until a clear solution resulted. On being kept overnight, the mixture solidified. After crystallisation, first from alcohol and then from 2-ethoxyethyl alcohol, the cyanide was obtained as colourless crystals (180 g.), m. p. 164—165° (Found : C, 72.3; H, 5.7; N, 10.1. $C_{17}H_{14}O_2N_2$ requires C, 72.85; H, 5.7; N, 10.0%).

3-Nitro-4-piperidino-1 : 2-diphenyl-*n*-butyl Cyanide (X).— α -Cyanostilbene (2.7 g.) was brought into reaction with methyl 2-nitroethyl ether (2.4 g.) in the presence of piperidine (1.75 g.) as described above for nitroethane. The product was collected, washed with methyl alcohol, and recrystallised repeatedly from acetone, giving colourless needles (2.9 g.), m. p. 171° (Found : C, 72.1; H, 6.65; N, 11.7. $C_{22}H_{20}O_2N_4$ requires C, 72.7; H, 6.9; N, 11.6%). The product was soluble in dilute acid and was reprecipitated unchanged by addition of sodium hydroxide.

3-Nitro-1 : 2-diphenyl-*n*-propyl Cyanide (VIII; R = H).— α -Cyanostilbene (38.5 g.), nitromethane (15 g.), and diethylamine (20 c.c.) were heated at 50° until a homogeneous solution resulted. After several days at 20°, the crystalline precipitate was collected, washed with ether, and recrystallised from alcohol, giving the cyanide as colourless prisms (5.5 g.), m. p. 94—96° (Found : N, 10.55. $C_{16}H_{14}O_2N_2$ requires N, 10.55%).

3-Nitro-2-phenyl-1-p-bromophenyl-*n*-butyl Cyanide (XIV).—Nitroethane (1.65 g.), 4-bromo- α -cyanostilbene (5.7 g.), Frost, *Annalen*, 1889, 250, 161) and piperidine (1.75 g.) were mixed and kept at 20° for 3 days. The semi-solid mass was then dissolved in hot methyl alcohol (10 c.c.) and allowed to cool. The crystalline product was collected (3.35 g.) and purified by repeated recrystallisation from alcohol, giving colourless crystals of the cyanide, m. p. 187—189° (Found : C, 56.65; H, 4.2; N, 8.05; Br, 21.75. $C_{17}H_{14}O_2N_2Br$ requires C, 56.8; H, 4.2; N, 7.8; Br, 22.3%).

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[Received, January 23rd, 1947.]

294. Aliphatic Nitro-compounds. Part XV. Preparation of Heterocyclic Bases by Reduction of 3-Nitroalkyl Cyanides.*

By G. D. BUCKLEY and T. J. ELLIOTT.

Reduction of 3-nitro-3-methyl-*n*-butyl cyanide (I) with iron and hydrochloric acid gives a mixture of 5-amino-2 : 2-dimethylpyrroline *N*-oxide (II) [or its tautomeride (IIa)], with 5-amino-2 : 2-dimethylpyrrolidine (III) [or its tautomeride (IIIa)]. The structure of (III) is established by formation from it of mono- and di-benzoyl derivatives, and by its hydrolysis to 5 : 5-dimethyl-2-pyrrolidone (V) by water and Raney nickel. The structure of the *N*-oxide (II) follows from its reduction to (III) by zinc-dust distillation and to 2 : 2-dimethylpyrrolidine (IV) on catalytic hydrogenation. Similar reactions with analogues of (I) are described, and possible mechanisms are discussed.

WITH a view to the synthesis of 3-amino-3-methyl-*n*-butyl cyanide, 3-nitro-3-methyl-*n*-butyl cyanide (I) was reduced with iron and hydrochloric acid. Two products were obtained : (a) a crystalline solid, $C_6H_{13}ON_2$, m. p. 238° (17% yield), and (b) a crystalline volatile base, $C_6H_{12}N_2$, (30% yield), with a formula and equivalent weight in agreement with those of the expected amino-cyanide, but with properties which excluded this structure.

The base, $C_6H_{12}N_2$, with 0.5 mol. of benzoyl chloride in ether gave a weakly basic monobenzoyl derivative which formed a picrate and was precipitated unchanged from its hydrochloric acid solution by addition of ammonia.

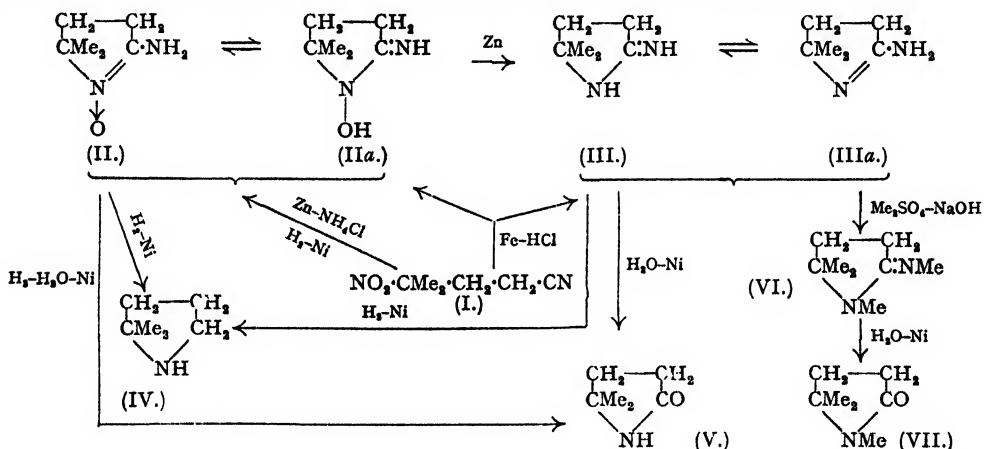
Benzoylation with excess of benzoyl chloride (Schotten-Baumann) gave both the monobenzoyl derivative and an acid-insoluble dibenzoyl derivative. This suggested that the base was the internal amidine 5-imino-2 : 2-dimethylpyrrolidine (III) [or 5-amino-2 : 2-dimethylpyrroline (IIIa)]. This was confirmed by the behaviour of the base on hydrolysis, reduction, and methylation. It was extremely resistant to acid or alkaline hydrolysis, but on boiling it with water in the presence of a little Raney nickel, ammonia was evolved and a crystalline, water-soluble solid $C_6H_{11}ON$, having the expected properties of 2 : 2-dimethyl-5-pyrrolidone (V), was formed. Reduction of the imine (III) with sodium and alcohol was difficult, but gave a small yield of 2 : 2-dimethylpyrrolidine (IV), also formed in good yield by catalytic reduction at 100°/100 atms. with Raney nickel under anhydrous conditions. Methylation of (III) with methyl sulphate and sodium hydroxide gave a dimethyl derivative, shown to be 5-methylimino-1 : 2 : 2-trimethylpyrrolidine (VI), by hydrolysis with water and Raney nickel to methylamine

* Patent application pending.

and 1 : 2 : 2-trimethyl-5-pyrrolidone (VII). The evidence in favour of the internal amidine structure (III) or (IIIa) is therefore conclusive.

Attention was then directed to the structure of the base $C_6H_{12}ON_2$ (above). This material was the main product when 3-nitro-3-methyl-*n*-butyl cyanide (I) was reduced with zinc dust and ammonium chloride under conditions which normally would be expected to reduce an aliphatic nitro-compound to the hydroxylamine, and was formed in 75% yield by reduction of (I) with hydrogen and Raney nickel at ordinary temperature and pressure. The base was weak; it gave a hydrochloride but would not react with benzoyl chloride, acetic anhydride, phenyl isocyanate, or *N*-nitro-*N'*-2 : 4-dinitrophenylurea. It contained two active hydrogen atoms (Zerewitinoff). Distillation with zinc dust gave the iminopyrrolidine (III), and reduction with sodium and alcohol gave a mixture of (III) and 2 : 2-dimethylpyrrolidine (IV). The latter was also formed by catalytic hydrogenation of the base $C_6H_{12}ON_2$ under anhydrous conditions at 100°/100 atms., but in the presence of water the pyrrolidone (V) was obtained in good yield, presumably by hydrolysis of the first-formed imine (III). Attempts to hydrolyse the base itself by boiling it with water and Raney nickel were unsuccessful.

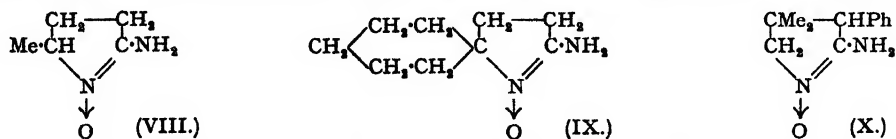
On this evidence the compound was formulated as 5-amino-2 : 2-dimethylpyrroline *N*-oxide (II) [or the tautomeric 5-imino-1-hydroxy-2 : 2-dimethylpyrrolidine (IIa)], and its formation is ascribed to cyclisation of the first-formed 3-hydroxylamino-3-methyl-*n*-butyl cyanide. A similar case has been reported by Bauer (*Ber.*, 1938, 71, 2226), who hydrogenated *o*-nitrostyryl cyanide over a palladium catalyst and obtained 2-aminoquinoline *N*-oxide in 60% yield.



In the reduction of the nitro-cyanide (I) with iron and hydrochloric acid, the iminopyrrolidine (III) might be formed either by reduction of the *N*-oxide (II) or by reduction of the nitro-cyanide to amino-cyanide, followed by cyclisation. Although difficult to prove conclusively, the former appears to be the more probable route; a careful search failed to reveal any amino-cyanide in the reduction products of (I), and it has been shown that the *N*-oxide (II) is, in fact, slowly reduced to the iminopyrrolidine (III) by iron and hydrochloric acid.

Attempts to reduce 3-nitro-3-methyl-*n*-butyl cyanide with platinum or palladium catalysts in the presence of mineral acids were unsuccessful, and use of stannous chloride and hydrochloric acid resulted in hydrolysis. It was concluded, therefore, that the preparation of 3-amino-3-methyl-*n*-butyl cyanide by reduction of the nitro-cyanide was impracticable.

Analogues of (I) were obtained, usually in good yield, by catalytic reduction of other 3-nitroalkyl cyanides. 3-Nitro-*n*-butyl cyanide gave 5-amino-2-methylpyrroline *N*-oxide (VIII), 1-nitro-1-(2-cyanoethyl)cyclohexane gave 5-amino-2 : 2-pentamethylenepyrroline *N*-oxide (IX),



and 3-nitro-1-phenyl-2 : 2-dimethyl-*n*-propyl cyanide gave 2-amino-3-phenyl-4 : 4-dimethylpyrroline *N*-oxide (X). Results of hydrogenations at 100 atms. were similar to those obtained

at atmospheric pressure. Raney nickel and palladised calcium carbonate appeared to be equally effective as catalysts, but Adams's platinum oxide gave inferior yields.

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. M. ps. are uncorrected. The nitro-cyanides were prepared by the methods described in Parts XIII and XIV of this series.

Reduction of 3-Nitro-3-methyl-n-butyl Cyanide.—(a) *With iron and hydrochloric acid.* Iron filings (30–60 mesh) (70 g.), water (150 c.c.), and hydrochloric acid (20 c.c. of 35%) were stirred together until the solution was no longer acid to Congo-red. The mixture was then heated to 100° and a solution of 3-nitro-3-methyl-n-butyl cyanide (47.5 g.) in alcohol (100 c.c.) was run in during 1 hour. The mixture was stirred and refluxed for 18 hours, cooled, and the filtered solution acidified to Congo-red with hydrochloric acid. The alcohol was distilled under reduced pressure, the residue diluted with sufficient water to dissolve the salts, and washed with ether. The aqueous solution was made strongly alkaline with potassium hydroxide and extracted repeatedly with ether (see later). The aqueous alkaline solution was then treated with solid potassium hydroxide and the precipitate collected and dissolved in a little water. Dilute hydrochloric acid was added until the solution was no longer alkaline to Clayton-yellow, and, after evaporation under reduced pressure, the product was isolated by extraction with absolute alcohol, evaporation of the extract and treatment with acetone giving 5-amino-2 : 2-dimethylpyrroline N-oxide (II) (8.0 g.) as a crystalline solid, which separated from alcohol-acetone in colourless plates, m. p. 238° (Found : C, 56.35; H, 9.45; N, 22.15. $C_6H_{12}ON_2$ requires C, 56.25; H, 9.4; N, 21.9%). The product was very soluble in water, chloroform, and alcohol, insoluble in ether, acetone, ethyl acetate, dioxan, and hydrocarbons. The hydrochloride had m. p. 173° (Found : Cl, 21.75. $C_6H_{12}ON_2 \cdot HCl$ requires Cl, 21.6%). The picrate, m. p. 160°, formed yellow needles from alcohol (Found : N, 20.0. $C_6H_{12}ON_2 \cdot C_6H_3O_7N_3$ requires N, 19.6%).

The ethereal extract was dried (KOH) and distilled, giving 5-imino-2 : 2-dimethylpyrrolidine (III) as colourless crystals (14.4 g.), b. p. 108–110°/15 mm., m. p. 73–74° [Found : *M* (by titration with 0.1N-hydrochloric acid to bromophenol-blue), 113.2. $C_6H_{12}N_2$ requires *M*, 112]. The picrate, m. p. 203–204°, formed yellow needles from alcohol (Found : N, 20.4. $C_6H_{12}N_2 \cdot C_6H_3O_7N_3$ requires N, 20.5%).

A solution of benzoyl chloride (0.6 g.) in dry ether (5 c.c.) was cautiously added to a solution of 5-imino-2 : 2-dimethylpyrrolidine (1 g.) in dry ether (5 c.c.). A vigorous reaction occurred, and after evaporation of the solvent the product was extracted with dilute aqueous ammonia and crystallised from 50% aqueous alcohol, giving the monobenzoyl derivative (0.6 g.) as colourless prisms, m. p. 98°, soluble in dilute hydrochloric acid and reprecipitated unchanged by addition of ammonia (Found : C, 72.0; H, 7.15; N, 12.65. $C_{12}H_{16}ON_2$ requires C, 72.2; H, 7.4; N, 12.95%).

Benzoyl chloride (6 g.) was added dropwise to a stirred and ice-cooled mixture of 5-imino-2 : 2-dimethylpyrrolidine (2 g.), sodium hydroxide (3.2 g.), and water (25 c.c.) at 10–15°. The mixture was stirred at 10–20° until the excess of benzoyl chloride had decomposed, and the precipitate was then collected, washed with water, and extracted with cold N-hydrochloric acid (50 c.c.). Treatment of the extract with aqueous ammonia precipitated a monobenzoyl derivative, identical with that described above. The acid-insoluble portion (3.2 g.) was repeatedly crystallised from acetone, giving colourless needles (0.3 g.), m. p. 179° (Found : C, 69.75; H, 5.65; N, 9.05%). This material was not further investigated. The acetone mother liquors were evaporated and the residue crystallised from alcohol, giving colourless needles of 5-benzimidazo-1-benzoyl-2 : 2-dimethylpyrrolidine, m. p. 133° (Found : C, 74.65; H, 6.6; N, 8.7. $C_{20}H_{26}O_2N_4$ requires C, 75.0; H, 6.25; N, 8.75%).

(b) *With zinc dust and ammonium chloride.* Zinc dust (25 g.) was added during 2½ hours to a vigorously stirred mixture of 3-nitro-3-methyl-n-butyl cyanide (20 g.), ammonium chloride (6 g.), and water (80 c.c.) at 10–15°. When reaction was complete the solution was filtered, neutralised with hydrochloric acid, evaporated under reduced pressure, and the residue extracted with absolute alcohol; the extract on dilution with dry ether gave the hydrochloride, m. p. 173°, of 5-amino-2 : 2-dimethylpyrroline N-oxide, from which the base, m. p. 238°, was obtained by basification.

(c) *Catalytically.* 3-Nitro-3-methyl-n-butyl cyanide (150 g.), dissolved in methyl alcohol (1500 c.c.), was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption of hydrogen ceased. The filtered solution was concentrated, finally by heating at 100°/20 mm., and the residue treated with acetone, giving 5-amino-2 : 2-dimethylpyrroline N-oxide. A second crop was obtained by concentrating the mother liquor and again treating the residue with acetone. The total yield was 101 g. (75%).

Reduction of 5-Amino-2 : 2-dimethylpyrroline N-Oxide.—(a) *Catalytically.* A solution of 5-amino-2 : 2-dimethylpyrroline N-oxide (10 g.) in anhydrous methanol (100 c.c.) was stirred with hydrogen and water and Raney nickel (1 g.) in an autoclave at 100°/100 atms. until absorption was complete, cooled, filtered from catalyst, and steam-distilled until free from volatile bases. The distillate was acidified with hydrochloric acid and evaporated to dryness. The hydrochloride was treated with a large excess of 40% aqueous potassium hydroxide, the base extracted with ether, the extract dried (KOH), and fractionated, giving 2 : 2-dimethylpyrrolidine (IV) (4.9 g.) as a colourless liquid, b. p. 105–106° (Found : *M* (by titration with 0.1N-hydrochloric acid to bromophenol-blue), 100.2. $C_6H_{12}N_2$ requires *M*, 99). The picrate, m. p. 190–191°, formed yellow needles from water (Found : N, 17.5. $C_6H_{12}N_2 \cdot C_6H_3O_7N_3$ requires N, 17.1%). The 2 : 4-dinitrophenylcarbonyl derivative (cf. McVeigh and Rose, *J.*, 1945, 621), m. p. 131°, formed long yellow needles from alcohol (Found : C, 50.65; H, 5.25; N, 18.2. $C_{11}H_{14}O_2N_4$ requires C, 50.65; H, 5.2; N, 18.2%).

(b) *With sodium and alcohol.* 5-Amino-2 : 2-dimethylpyrroline N-oxide (75 g.) was dissolved in absolute alcohol (2 l.) and treated rapidly at the boil with sodium (170 g.). When the sodium was completely dissolved, the solution was cooled and cautiously acidified to Congo-red with concentrated hydrochloric acid, filtered from salt and steam-distilled. The residual solution was diluted with an equal volume of 32% aqueous sodium hydroxide and extracted with ether. The extract, after drying

and distillation, yielded 5-imino-2 : 2-dimethylpyrrolidine (14.2 g.). The steam-distillate was acidified with hydrochloric acid and evaporated to dryness, leaving a hydrochloride, which, after basification and distillation, yielded 2 : 2-dimethylpyrrolidine (7.2 g.).

(c) *By distillation with zinc dust.* 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (30 g.) was mixed thoroughly with zinc dust (30 g.) and heated, 20 g. at a time, in a distillation apparatus under 20 mm. The bath was heated to 280° and the temperature was then slowly raised to 320° and held at this until distillation ceased. The distillate was extracted with ether and the extract dried (KOH) and fractionated giving 5-imino-2 : 2-dimethylpyrrolidine (7 g.), b. p. 106°/15 mm.

(d) *With iron and hydrochloric acid.* 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (20 g.) was reduced for 48 hours at 95–100° with iron (35 g.) and hydrochloric acid as described above for the reduction of the nitro-cyanide. Isolation as before gave 5-imino-2 : 2-dimethylpyrrolidine (7.9 g.), together with much unchanged starting materials.

Reduction of 5-Imino-2 : 2-dimethylpyrrolidine.—(a) *Catalytically.* The base (5 g.) was hydrogenated at 100°/100 atms. under anhydrous conditions as described above for 5-amino-2 : 2-dimethylpyrroline *N*-oxide. The resulting solution was filtered and fractionated, giving 2 : 2-dimethylpyrrolidine (1V) (3.8 g.); picrate, m. p. 190–191°.

(b) *With sodium and alcohol.* 5-Imino-2 : 2-dimethylpyrrolidine (7 g.) was reduced with sodium (50 g.) and absolute alcohol (600 c.c.) as described above for the pyrroline oxide. The product was worked up as before to give a small amount of 2 : 2-dimethylpyrrolidine, together with unchanged 5-imino-2 : 2-dimethylpyrrolidine (3.2 g.).

2 : 2-Dimethyl-5-pyrrolidone (V).—(a) A solution of 5-imino-2 : 2-dimethylpyrrolidine (3 g.) in water (30 c.c.) was stirred and refluxed for 3 hours with Raney nickel (0.1 g.); ammonia was evolved. The filtered solution was distilled, giving 2 : 2-dimethyl-5-pyrrolidone (2.1 g.) as colourless, hygroscopic crystals, m. p. 42°, b. p. 140°/20 mm. (Found : C, 63.4; H, 9.7; N, 12.15. $C_6H_{11}ON$ requires C, 63.7; H, 9.75; N, 12.4%). The hydrochloride had m. p. 150–152° (Found : Cl, 23.4. $C_6H_{11}ON \cdot HCl$ requires Cl, 23.75%).

(b) 5-Amino-2 : 2-dimethylpyrroline *N*-oxide (5 g.), dissolved in methyl alcohol (100 c.c.), was stirred with Raney nickel and hydrogen at 100°/100 atms. until absorption of hydrogen ceased. Distillation of the product gave 2 : 2-dimethyl-5-pyrrolidone (3.2 g.).

Methylation of 5-Imino-2 : 2-dimethylpyrrolidine.—Methyl sulphate (40 g.) was added dropwise to a stirred and cooled mixture of 5-imino-2 : 2-dimethylpyrrolidine (10 g.) and aqueous sodium hydroxide (80 c.c. of 16%) at 10–15°. The mixture was stirred at 10–20° until the excess of methyl sulphate had decomposed, and was then treated with an equal volume of 32% sodium hydroxide solution and extracted with ether. The extract was dried (KOH) and distilled, giving 5-methylimino-1 : 2 : 2-trimethylpyrrolidine (VI) (11 g.) as a colourless oil, b. p. 97–98°/18 mm. The picrate, m. p. 125°, formed yellow needles from water (Found : C, 46.2; H, 5.1; N, 19.25. $C_8H_{16}N_2 \cdot C_6H_5O_7N_3$ requires C, 45.55; H, 5.15; N, 19.0%).

1 : 2 : 2-Trimethyl-5-pyrrolidone (VII).—The base (above) (6.8 g.) in water (70 c.c.) was boiled with Raney nickel for 3 hours. An aqueous solution of the evolved gases was shown to be free from ammonia (no precipitate with Nessler's reagent), but, on boiling with *N*-nitro-*N'*-2 : 4-dinitrophenylurea, gave *N*-2 : 4-dinitrophenyl-*N'*-methylurea, m. p. and mixed m. p. with an authentic specimen, 204° (cf. McVeigh and Rose, *loc. cit.*). The aqueous residue was filtered from catalyst and distilled, giving 1 : 2 : 2-trimethyl-5-pyrrolidone (VII) (4.9 g.) as a colourless oil, b. p. 130°/60 mm. (Found : C, 66.2; H, 10.2; N, 10.95. $C_7H_{13}ON$ requires C, 66.1; H, 10.25; N, 11.05%).

5-Amino-2-methylpyrroline *N*-Oxide (VIII).—3-Nitro-*n*-butyl cyanide (32 g.) in methyl alcohol (400 c.c.) was hydrogenated in the presence of Raney nickel at 20°/1 atm. The filtered solution was concentrated and the residue was stirred with acetone and the solid collected (5 g.). Crystallisation from chloroform-acetone gave colourless, hygroscopic needles, m. p. 206° (Found : C, 52.65; H, 8.4; N, 24.3. $C_6H_{10}ON_2$ requires C, 52.65; H, 8.75; N, 24.55%).

5-Amino-2 : 2-pentamethylenepyrroline *N*-Oxide (IX).—1-Nitro-1-(2-cyanoethyl)cyclohexane (21 g.) was hydrogenated and the product (8 g.) isolated as described above. Crystallisation from acetone-alcohol gave the base as colourless leaflets, m. p. 206° (Found : N, 16.4. $C_8H_{14}ON_2$ requires N, 16.65%). The hydrochloride had m. p. 200° (Found : Cl, 17.45. $C_8H_{14}ON_2 \cdot HCl$ requires Cl, 17.3%).

2-Amino-3-phenyl-4 : 4-dimethylpyrroline *N*-Oxide (X).—3-Nitro-1-phenyl-2 : 2-dimethyl-*n*-propyl cyanide (5 g.), dissolved in methyl alcohol (50 c.c.), was shaken with hydrogen and 5% palladised calcium carbonate (1 g.) until absorption of hydrogen was complete. After filtration from catalyst, the solution was evaporated on the steam-bath and the residue was treated with acetone and collected (3 g.); crystallisation from acetone-alcohol gave colourless granules, m. p. 189–190° (Found : N, 13.7. $C_{12}H_{16}ON_2$ requires N, 13.7%).

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[Received, January 23rd, 1947.]

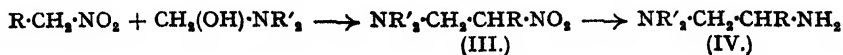
295. Aliphatic Nitro-compounds. Part XVI. Condensation of Hydroxymethyldialkylamines with Nitro-paraffins.

By A. LAMBERT and J. D. ROSE.

Hydroxymethyl derivatives of secondary amines and nitromethane or nitroethane yield, on heating, only nitro-diamines of type II ($R = H$ or Me). 1-Nitropropane gives chiefly the nitro-amine (III; $R = Et$) and a little nitro-diamine (I; $R = Et$). Nitro-amines (III; $R = Me$) are prepared from nitroethane and hydroxymethyldialkylamine by carrying out the

reaction for a short time at ordinary temperature. Reductions of the nitro-diamines and nitro-amines to triamines and diamines respectively are described.

IN connection with other synthetic work in progress in these laboratories, amines of the types (II) and (IV) were required, and it appeared probable that the simplest and most direct method of synthesis would be from nitro-paraffins and hydroxymethyl derivatives of secondary amines, followed by hydrogenation of the nitro-amine so formed.



Substances of type (I) ($R = H$ or Me) were prepared first by Henry (*Bull. Soc. chim.*, 1896, 15, 1225; *Ber.*, 1905, 38, 2027) from nitromethane and nitroethane with *N*-hydroxymethylpiperidine. Despite this, de Mauney (*Bull. Soc. chim.*, 1937, 4, 1451, 1460), as a result of experiments on the condensation of hydroxymethyl secondary amines with nitromethane, 1-nitropropane, 1-nitrobutane, and 1-nitro-octane, stated that the reaction product from primary nitro-paraffin always contained one free α -hydrogen atom, *i.e.*, nitromethane combines with two and other primary nitro-paraffins with only one mol. of hydroxymethylamine. As was shown by Zief and Mason (*J. Org. Chem.*, 1943, 8, 1), nitroethane is an exception to this rule as it condenses with *N*-hydroxymethylpiperidine (Henry, *loc. cit.*) and with *N*-hydroxymethylmorpholine to give compounds of type (I) ($R = Me$). Furthermore, although 1-nitropropane reacts with *N*-hydroxymethyldiethylamine to give mainly 2-nitro-1-diethylaminobutane (III; $R = R' = Et$), we have also obtained small yields of the bis-condensate, 2-nitro-1 : 3-bis(diethylamino)-2-ethylpropane, from this reaction.

The formation of amines of the type (III) ($R = Me$) from nitroethane is a matter of some difficulty. Attempts to degrade the bis-adducts of type (I) from nitroethane to mono-adducts of type (III) by alkaline reagents were uniformly unsuccessful, although this method is applicable to the degradation of, *e.g.*, tris(hydroxymethyl)nitromethane to 2-nitropropane-1 : 3-diol. Since 2-nitro-2-methylpropane-1 : 3-diol condenses with, *e.g.*, hydroxymethylpiperidine to give the nitro-diamine in good yield, an attempt was made to effect a similar reaction with 2-nitro-*n*-propyl alcohol. Disproportionation occurred, the only product isolated being 2-nitro-1 : 3-dipiperidino-2-methylpropane, formed by fission of the nitro-alcohol to nitroethane and formaldehyde, followed by recombination in the appropriate proportions. Similarly, 2-nitroethyl alcohol and piperidine yielded only 2-nitro-1 : 3-dipiperidinopropane, and 2-nitroisopropyl alcohol (from nitromethane and acetaldehyde), on treatment with hydroxymethylpiperidine, gave acetaldehyde and 2-nitro-1 : 3-dipiperidinopropane.

Finally, the nitro-monoamines of type (III) were obtained by allowing equimolecular proportions of the nitro-paraffin and the hydroxymethylamine to interact at room temperature. In this way, 2-nitro-1-diethylaminopropane was obtained in 70% yield from nitroethane and hydroxymethyldiethylamine, and 2-nitro-1-piperidinopropane was formed from nitroethane and hydroxymethylpiperidine. Although the nitro-amines were unstable and could not be obtained pure, and precipitated nitro-diamine on storage, reduction of the freshly prepared crude products gave the diamines (IV).

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

2-Nitro-1 : 3-dipiperidino-2-methylpropane.—(a) This was prepared from hydroxymethylpiperidine and nitroethane according to Henry (*loc. cit.*); white needles from alcohol, m. p. 102°. Henry (*loc. cit.*) gives m. p. 98—99° (Found: C, 62.3; H, 9.7; N, 15.3. Calc. for $C_{14}H_{24}O_2N_4$: C, 62.8; H, 10.0; N, 15.6%).

(b) A mixture of 2-nitro-2-methylpropane-1 : 3-diol (Vanderbilt and Hass; *Ind. Eng. Chem.*, 1940, 32, 34; 136 g.) and piperidine (170 g.) in alcohol (300 c.c.) was refluxed for 3 hours. After cooling, the crystals were collected, washed with a little alcohol, and dried, and had m. p. 102° alone and in admixture with a sample prepared as (a) above. Yield, 172 g.

2-Nitro-1 : 3-bis(diethylamino)-2-methylpropane.—Formaldehyde (40%; 75 c.c.) was treated with diethylamine (74 g.) in water (75 c.c.) at 0°, and to the mixture nitroethane (37 g.) was added with stirring at room temperature. After 16 hours' stirring the supernatant oil was isolated with ether, dried (K_2CO_3), and fractionated to give 2-nitro-1 : 3-bis(diethylamino)-2-methylpropane as an almost colourless liquid, b. p. 94—96°/0.2 mm. (Found: C, 58.8; H, 10.7; N, 16.6. $C_{18}H_{32}O_2N_4$ requires C, 58.8; H, 11.0; N, 17.1%). This diamine was unchanged by treatment with 1 mol. of sodium methoxide in methyl alcohol at room temperature. Catalytic hydrogenation with Raney nickel and hydrogen caused decomposition to low boiling products among which bis(diethylamino)methane was recognised.

2-Amino-1 : 3-bis(diethylamino)-2-methylpropane.—Crude 2-nitro-1 : 3-bis(diethylamino)-2-methylpropane, prepared as above (not distilled; total product after concentration of ethereal solution) from nitroethane (37 g.), was added dropwise with stirring to an ice-cold solution of stannous chloride (327 g.) in concentrated hydrochloric acid (500 c.c.). After 1 hours' stirring, excess of 30% aqueous sodium hydroxide was added and the product isolated with ether, dried (K_2CO_3), and fractionated. The fraction, b. p. 63–67°/0.2 mm., was dried over sodium and redistilled, giving the *amine* as a colourless oil, b. p. 60°/0.1 mm. (Found : N, 19.6. $C_{13}H_{29}N_3$ requires N, 19.5%).

2-Amino-1 : 3-bis(diethylamino)-2-ethylpropane.—A solution of diethylamine (73 g.) in water (75 c.c.) was added at 0° to formaldehyde (40%; 75 c.c.) and 1-nitropropane (45 g.) then added and the mixture stirred at room temperature for 20 hours. The upper layer was isolated with ether and distilled, giving chiefly 2-nitro-1-diethylaminobutane, b. p. 70°/0.4 mm. (cf. de Mauney, *loc. cit.*), and crude 2-nitro-1 : 3-bis(diethylamino)-2-ethylpropane (18 g.), b. p. 108°/0.2 mm., with slight decomposition (Found : N, 15.3. $C_{13}H_{29}O_2N_3$ requires N, 16.2%). This latter was reduced as described above for the lower homologue, with stannous chloride (60 g.) and hydrochloric acid (100 c.c.) at 0°, giving 2-amino-1 : 3-bis(diethylamino)-2-ethylpropane (5 g.) as a colourless oil, b. p. 112–114°/10 mm. (Found : C, 67.7; H, 12.8; N, 17.8. $C_{13}H_{31}N_3$ requires C, 68.1; H, 13.5; N, 18.3%). The *triplicate* formed yellow prisms from water, m. p. 162° (Found : C, 40.6; H, 4.4; N, 17.8. $C_{13}H_{31}N_3 \cdot 3C_2H_5O_7N_3$ requires C, 40.6; H, 4.4; N, 18.3%).

2-Nitro-1-diethylaminopropane.—Formaldehyde (40%; 8.1 c.c.) and diethylamine (7.3 g.) in water (10 c.c.) were mixed at 0° and nitroethane (7.5 g.) was added slowly with cooling. The mixture was kept at room temperature for 4 hours, extracted with ether, and the ethereal extract dried and distilled. 2-Nitro-1-diethylaminopropane was obtained as a pale yellow oil (11 g.), b. p. 83.5°/11 mm. (Found : C, 52.6; H, 10.1; N, 17.3. $C_7H_{15}O_2N_2$ requires C, 52.5; H, 10.0; N, 17.5%), which decomposed slowly on keeping.

2-Amino-1-diethylaminopropane.—The nitro-amine (above) was reduced in methyl-alcoholic solution with Raney nickel and hydrogen at 70 atmospheres (initial pressure) and room temperature. Fractionation of the filtered solution gave 2-amino-1-diethylaminopropane, b. p. 148–149°/772 mm., in 47% yield [Found : equiv. (by titration), 66.9. $C_8H_{18}N_2$ requires equiv., 65].

2-Amino-1-piperidinopropane.—Formaldehyde (87%; 81 c.c.), piperidine (85 g.), water (85 c.c.), and nitroethane (75 g.) were brought into reaction as described above for the diethylamino-analogue. 2-Nitro-1-piperidinopropane was obtained as an oil (142 g.), b. p. 99–104°/7 mm. (slight decomp.), and could not be obtained analytically pure. On keeping, decomposition occurred and 2-nitro-1 : 3-dipiperidino-2-methylpropane was precipitated. Reduction of the freshly prepared material (128 g.) with Raney nickel and hydrogen at 60 atms. and 40° gave 2-amino-1-piperidinopropane as a colourless oil (54 g.), b. p. 92–93°/15 mm. (Found : equiv. by titration), 71.4. Calc. for $C_8H_{18}N_2$: equiv., 71). Wenker (*J. Amer. Chem. Soc.*, 1938, 60, 158), who prepared this compound by amination of 2-chloro-1-piperidinopropane, gives b. p. 193–194°/760 mm.).

Reaction of 2-Nitroethyl Alcohol with Piperidine.—2-Nitroethyl alcohol (10 g.), piperidine (20 c.c.), and dioxan (20 c.c.) were refluxed for 20 minutes and poured into water. The product was mainly 2-nitro-1 : 3-dipiperidinopropane, m. p. 93–94°, undepressed by admixture with an authentic specimen prepared from nitromethane and hydroxymethylpiperidine (Henry, *loc. cit.*).

Reaction of 2-Nitro-*n*-propyl Alcohol with Piperidine.—2-Nitro-*n*-propyl alcohol (21 g.) and piperidine (17 g.) were mixed; there was considerable heat evolution and the mixture was warmed on the steam-bath for one hour. On cooling, the dark liquor deposited crystals, which were collected and recrystallised from alcohol, giving 2-nitro-1 : 3-dipiperidino-2-methylpropane, m. p. 104° alone and in admixture with an authentic specimen.

Reaction of 2-Nitroisopropyl Alcohol with Piperidine and Formaldehyde.—2-Nitroisopropyl alcohol (10.5 g.) and piperidine (17.0 g.) were mixed and cooled, and formaldehyde (15 c.c.) was added. A pronounced smell of acetaldehyde became apparent and a crystalline solid separated. Recrystallised from alcohol, this gave 2-nitro-1 : 3-dipiperidinopropane, m. p. 93–94° alone and in admixture with an authentic specimen.

2 : 2'-Dipiperidinoisopropylamine.—2-Nitro-1 : 3-dipiperidinopropane (200 g.) in methyl alcohol (750 c.c.) was reduced with Raney nickel and hydrogen at 130 atms. (initial pressure) and 50°. Distillation of the filtered solution yielded 2 : 2'-dipiperidinoisopropylamine, b. p. 152–154°/11 mm. Yield, 124 g. (70%) (Found : C, 68.6; H, 11.9; N, 18.4. $C_{13}H_{27}N_3$ requires C, 69.3; H, 12.0; N, 18.6%). The *trihydrochloride* formed pearly plates from aqueous alcohol, m. p. 260° (Found : Cl, 31.7. $C_{13}H_{27}N_3 \cdot 3HCl$ requires Cl, 31.8%).

2 : 2'-Dipiperidinoisopropylurea.—The amine (8 g.), suspended in boiling water (100 c.c.), was treated cautiously with nitrourea; 11 g. (3 mols.) were necessary to give a clear solution. The filtered solution was treated with an excess of 10*N*-sodium hydroxide; the precipitated oil solidified immediately and was recrystallised from acetone. The *urea* had m. p. 86° (Found : C, 62.3; H, 10.3. $C_{14}H_{28}ON_4$ requires C, 62.6; H, 10.4%). The *dimethiodide*, from aqueous alcohol, had m. p. 257° (decomp.) (Found : N, 9.6; I, 45.7. $C_{14}H_{34}ON_4I_2$ requires N, 10.1; I, 46.0%).

The authors wish to acknowledge the interest and advice of Mr. C. Paine and Dr. H. A. Piggott in this work.

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[Received, January 23rd, 1947.]

296. Aliphatic Nitro-compounds. Part XVII. Reaction of Nitro-paraffins with Unsaturated Sulphones.*

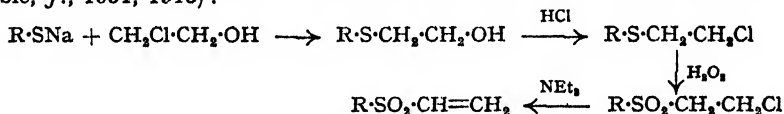
By G. D. BUCKLEY, (MRS.) J. L. CHARLISH, and J. D. ROSE.

Nitro-paraffins react with vinyl sulphones in the presence of alkaline catalysts to yield 3-nitroalkyl sulphones. The use of small amounts of catalyst results in the replacement of all the α -hydrogen atoms of the nitro-paraffin to give nitro-monosulphones from secondary nitro-paraffins, nitro-disulphones from primary nitro-paraffins, and nitro-trisulphones from nitromethane. The use of sufficient alkali to convert the whole of the nitro-paraffin into its salt results in the formation of mainly mononitro-sulphones from primary nitro-paraffins. 2-Halogenoethyl sulphones with an equivalent of alkali may be used in place of vinyl sulphones. Divinyl sulphone reacts in a similar manner: with secondary nitro-paraffins it gives 3:3'-dinitrodialkyl sulphones, but with primary nitro-paraffins the products are polymeric. Catalytic reduction of the nitro-sulphones affords the corresponding amino-sulphones, and their alkali metal salts give 3-keto-sulphones on treatment with mineral acids.

A convenient synthesis of vinyl sulphones is described.

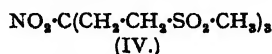
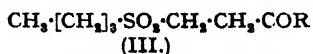
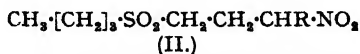
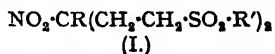
PREVIOUS authors have described the addition of primary and secondary nitro-paraffins to $\alpha\beta$ -unsaturated nitro-compounds (this series, Part VIII), cyanides (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, 65, 23), and ketones and esters (Kohler, *J. Amer. Chem. Soc.*, 1916, 38, 889; Sonn, *Ber.*, 1935, 68, 148; Michael, *Ber.*, 1896, 29, 1794), but no attempt to cause them to react with vinyl sulphones appears to have been recorded.

Although divinyl sulphone is a well-known compound, the simple monovinyl sulphones appear to be described only in the patent literature (B.P. 442,524, I.G. Farbenindustrie). Since the method described seemed unsuitable for use on the laboratory scale, the monovinyl sulphones were prepared by the following route based on the usual synthesis of divinyl sulphone (Alexander and McCombie, *J.*, 1931, 1913):



This method gave *methyl*, *n-butyl*, *isobutyl*, and *p-tolyl* vinyl sulphones in satisfactory yield.

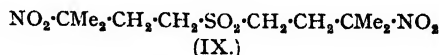
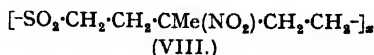
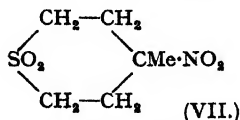
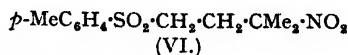
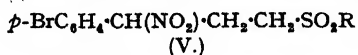
Nitroethane reacted readily with two molecules of *n-butyl* vinyl sulphone in presence of a small amount of potassium hydroxide to give a 75% yield of 3-nitro-1:5-di-(*n-butylsulphonyl*)-3-methylpentane (I; R = Me, R' = Bu) which was reduced catalytically to the corresponding amine. In presence of one equivalent of sodium hydroxide, nitroethane reacted with one molecule of *n-butyl* vinyl sulphone to give 3-nitrodibutyl sulphone (II; R = Me) in 45% yield, together with a 13% yield of the dinitrosulphone (I; R = Me, R' = Bu). It was not possible to suppress completely the formation of the dinitrosulphone even by the use of a large excess of alkali. 3-Nitrodibutyl sulphone was isolated as an oil by acidification of the alkaline solution with acetic or carbonic acids, but acidification with mineral acids precipitated 3-ketodibutyl sulphone (III; R = Me), formed by a Nef hydrolysis (*Annalen*, 1894, 280, 263), which appears to be unusually facile in the case of γ -nitro-sulphones. The nitro-sulphone could not be purified by distillation or crystallisation, but was reduced catalytically to the easily characterised 3-aminodibutyl sulphone (*hydrochloride*).



Similarly, 1-nitropropane reacted with *n-butyl* vinyl sulphone to give 3-nitro-1:5-di-(*n-butylsulphonyl*)-3-ethylpentane (I; R = Et, R' = Bu), *n-butyl* 3-nitroamyl sulphone (II; R = Et), and *n-butyl* 3-ketoamyl sulphone (III; R = Et). Reaction of the sodium salt of *n-butyl* 3-nitroamyl sulphone with aqueous bromine gave *n-butyl* 3-bromo-3-nitroamyl sulphone. Interaction of nitromethane and methyl vinyl sulphone in presence of a little potassium hydroxide gave a 50% yield of *tris*-(2-methylsulphonylethyl)nitromethane (IV), which was reduced catalytically to *tris*-(2-methylsulphonylethyl)methylamine. *p*-Bromophenylnitromethane with methyl vinyl sulphone and a little methyltriethylammonium hydroxide gave *methyl* 3-nitro-3-*p-bromophenylpropyl* sulphone (V; R = Me) in 50% yield, and the sodium salt of

* Patent application pending.

p-bromophenylnitromethane reacted with isobutyl vinyl sulphone to give isobutyl 3-nitro-3-*p*-bromophenylpropyl sulphone (V; R = CH₂·CHMe₂) in 30% yield. 1- and 2-Nitropropane with *p*-tolyl vinyl sulphone gave respectively 3-nitro-1:5-di-*p*-tolylsulphonyl-3-ethylpentane (I; R = Et, R' = *p*-MeC₆H₄) and 2-nitro-4-*p*-tolylsulphonyl-2-methylbutane (VI).



The behaviour of divinyl sulphone was next examined. It was hoped that interaction of equimolecular proportions of nitroethane and divinyl sulphone would yield the cyclic sulphone (VII), but although a variety of conditions were tried the only products isolated were polymeric, presumably of type (VIII). The expected cyclisation is apparently hindered by steric factors. Divinyl sulphone reacted normally with two molecules of 2-nitropropane to give 3:3'-dinitro-3:3'-dimethyldibutyl sulphone (IX) which, on catalytic reduction, gave 3:3'-diamino-3:3'-dimethyldibutyl sulphone.

Experiments with 2-chloroethyl *n*-butyl sulphone showed that 2-halogenoethyl sulphones with an equivalent of sodium hydroxide could be used instead of vinyl sulphones, but the yields were lower, e.g., 1-nitropropane reacted with 2-chloroethyl *n*-butyl sulphone to give 8% of 3-nitro-1:5-di-(*n*-butylsulphonyl)-3-ethylpentane (I; R = Et, R' = Bu) and 32% of *n*-butyl 3-nitroamyl sulphone (II; R = Et).

EXPERIMENTAL

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

Preparation of Alkyl Vinyl Sulphones.

Methyl Vinyl Sulphone.—Hydrogen peroxide (300 g. of 30%) was added dropwise to a solution of methyl 2-chloroethyl sulphide (135 g.) (*Org. Synth.*, Coll. Vol. 2, 136) in acetic acid (300 c.c.) at such a rate that the solution refluxed gently without external heating. After a further 3 hours' heating on the steam-bath, the solvents were removed by distillation under reduced pressure. The viscous residue, consisting essentially of methyl 2-chloroethyl sulphone, was added during 1 hour to a stirred solution of triethylamine (175 c.c.) in anhydrous ether (320 c.c.) and the mixture was stirred for a further 18 hours. The ethereal solution was decanted from the dark mass of triethylamine hydrochloride which was then extracted with dry acetone. The ether and acetone solutions were combined and fractionated to give methyl vinyl sulphone as a colourless oil (81 g.), b. p. 115–117°/19 mm. (Found: S, 29.8. C₃H₆O₂S requires S, 30.2%).

***n*-Butyl Vinyl Sulphone.**—2-Chloroethyl *n*-butyl sulphone was prepared by oxidation of the corresponding sulphide according to Whitner and Reid (*J. Amer. Chem. Soc.*, 1921, **43**, 637). The crude sulphone (158 g.) was added during 1 hour to a stirred solution of triethylamine (135 c.c.) in ether (250 c.c.) and the mixture was stirred for a further 18 hours. The solution was then filtered from triethylamine hydrochloride and distilled to give *n*-butyl vinyl sulphone as a colourless oil (104 g.), b. p. 135°/15 mm. (Found: S, 21.3. C₆H₁₂O₂S requires S, 21.6%).

isobutyl Vinyl Sulphone.—Ethylene chlorohydrin (99 g. of 30%) was added to a suspension of isobutylthiol (37 g.) in aqueous sodium hydroxide (115 g. of 15%) and refluxed for 1 hour. The mixture was then freed from volatile impurities by steam distillation and, after cooling, the residual oil, consisting of crude 2-hydroxyethyl isobutyl sulphide (40 g.), was separated, mixed with concentrated hydrochloric acid (60 c.c.) and refluxed for 4 hours. After cooling, the oily product was separated, dried (CaCl₂), and distilled, giving 2-chloroethyl isobutyl sulphide as a vesicant oil (39 g.), b. p. 84–85°/25 mm. (Found: Cl, 23.1. C₆H₁₂ClS requires Cl, 23.3%). The chloroethyl sulphide (38 g.) was oxidised to 2-chloroethyl isobutyl sulphone and this was converted into the vinyl sulphone as described above for the isomer. isobutyl vinyl sulphone was obtained as a colourless oil (22 g.), b. p. 132–133°/19 mm. Found: S, 21.8. C₆H₁₂O₂S requires S, 21.6%).

***p*-Tolyl Vinyl Sulphone.**—Hydrogen peroxide (145 g. of 30%) was added slowly to a boiling solution of *p*-tolyl 2-chloroethyl sulphide (36 g.) (Kohn and Fromm, *Ber.*, 1921, **54**, 322) in acetic acid (105 c.c.) and the mixture was refluxed for 2 hours. Water and acetic acid were removed under reduced pressure, and the residual crude *p*-tolyl 2-chloroethyl sulphone (42 g.) was dissolved in dry ether (80 c.c.) and added cautiously to a solution of triethylamine (40 c.c.) in dry ether (80 c.c.). Separation of triethylamine hydrochloride began at once, and, after standing overnight, the solution was filtered and evaporated to dryness. The residue was washed with cold water, giving a white, crystalline solid (25 g.) which, after crystallisation from alcohol, gave *p*-tolyl vinyl sulphone as white needles, m. p. 66° (I.G. Farbenindustrie, *loc. cit.*, give m. p. 65–66°).

Reaction with Nitro-paraffins.

3-Nitro-1:5-di-(*n*-butylsulphonyl)-3-methylpentane.—Aqueous potassium hydroxide (1 c.c. of 33%) was added to a solution of nitroethane (3.5 g.) and *n*-butyl vinyl sulphone (15 g.) in alcohol (40 c.c.) and refluxed for 16 hours. After cooling, the precipitate was collected (13.25 g.) and crystallised from

alcohol, giving 3-nitro-1:5-di-(*n*-butylsulphonyl)-3-methylpentane (I; R = Me, R' = Bu) as colourless needles, m. p. 105° (Found: N, 4.1; S, 17.1. $C_{14}H_{28}O_6NS_2$ requires N, 3.8; S, 17.25%).

3-Nitrodibutyl Sulphone.—Aqueous sodium hydroxide (20 c.c. of 32%) was slowly added to a stirred and ice-cooled mixture of nitroethane (15 g.) and water (80 c.c.). When a homogeneous solution had formed, *n*-butyl vinyl sulphone (30 g.) was added and the mixture stirred at 20° for 3 hours. The solid precipitate (10 g.) was collected and washed with water; it was identical with the 3-nitro-1:5-di-(*n*-butylsulphonyl)-3-methylpentane described above. The alkaline filtrate was washed with ether to remove impurities, acidified with acetic acid (13 c.c.), and extracted with ether. The ethereal extract was dried and evaporated, leaving 3-nitrodibutyl sulphone (II; R = Me) as a pale yellow oil (21 g.) which could not be crystallised and decomposed on attempted distillation. With nitrous acid it gave a blue colouration, indicating the presence of a secondary nitro-group.

3-Aminodibutyl Sulphone.—Crude 3-nitrodibutyl sulphone (23 g.) in methyl alcohol (200 c.c.) was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased. The filtered solution was distilled, giving 3-aminodibutyl sulphone (8.6 g.) as a colourless, feebly basic oil, b. p. 122°/0.5 mm. The hydrochloride formed colourless granules, m. p. 145° (Found: Cl, 15.8. $C_8H_{18}O_2NS.HCl$ requires Cl, 15.55%). The phenylurea formed colourless granules from benzene, m. p. 107° (Found: N, 9.15; S, 10.1. $C_{11}H_{20}O_2N_2S$ requires N, 9.0; S, 10.25%).

3-Ketodibutyl Sulphone (III; R = Me).—A solution of the sodium salt of 3-nitrodibutyl sulphone, prepared from nitroethane (3.75 g.) and *n*-butyl vinyl sulphone (7.5 g.) as described above, was run into a stirred solution of sulphuric acid (6.5 c.c.) in water (30 c.c.) during 30 minutes, the temperature being kept at 10–15°. The crystalline precipitate was collected (3.8 g.) and recrystallised from a little methyl alcohol at –20°, giving the ketone as colourless plates, m. p. 59° (Found: S, 16.6. $C_8H_{16}O_3S$ requires S, 16.65%). The 2:4-dinitrophenylhydrazones, m. p. 147°, formed yellow needles from alcohol (Found: N, 14.85; S, 8.6. $C_{14}H_{20}O_6N_4S$ requires N, 15.05; S, 8.6%).

3-Amino-1:5-di-(*n*-butylsulphonyl)-3-methylpentane.—3-Nitro-1:5-di-(*n*-butylsulphonyl)-3-methylpentane (5.8 g.) was suspended in 2-ethoxyethyl alcohol (100 c.c.) and shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption ceased; during the reaction the solid gradually passed into solution. The filtered solution was concentrated under reduced pressure and the residue crystallised from benzene, giving colourless crystals of the amine, m. p. 116° (Found: N, 4.1; S, 19.1. $C_{14}H_{28}O_6NS_2$ requires N, 4.15; S, 18.8%). The acetyl derivative formed colourless needles from water, m. p. 164° (Found: S, 16.35. $C_{14}H_{28}O_6NS_2$ requires S, 16.7%).

3-Nitro-1:5-di-(*n*-butylsulphonyl)-3-ethylpentane and *n*-Butyl 3-Nitroamyl Sulphone.—(a) From *n*-butyl vinyl sulphone. Aqueous sodium hydroxide (5 c.c. of 32%) was slowly added to a stirred and ice-cooled mixture of 1-nitropropane (4.5 g.) and water (20 c.c.). When the oil had completely dissolved, *n*-butyl vinyl sulphone (7.5 g.) was added and the mixture was stirred at 50° for 3 hours. After cooling, the solid product was collected (1.65 g.). Crystallisation from alcohol gave 3-nitro-1:5-di-(*n*-butylsulphonyl)-3-ethylpentane (I; R = Et, R' = Bu) as colourless needles, m. p. 104° (Found: N, 3.9; S, 16.8. $C_{15}H_{31}O_6NS_2$ requires N, 3.65; S, 16.6%). The alkaline filtrate was washed with ether, acidified with acetic acid (3.5 c.c.), extracted with ether, and the dried extract concentrated, giving *n*-butyl 3-nitroamyl sulphone (II; R = Et) as a pale yellow oil (6 g.) which could not be purified by crystallisation or distillation. With nitrous acid it gave a positive test for a secondary nitro-group.

(b) From 2-chloroethyl *n*-butyl sulphone. Aqueous sodium hydroxide (12 c.c. of 32%) was added slowly to an ice-cold solution of 1-nitropropane (4.5 g.) in methyl alcohol (20 c.c.). 2-Chloroethyl *n*-butyl sulphone (9.3 g.) was then added and the mixture was stirred at 20° for 18 hours. The solution was diluted with water (50 c.c.) and the precipitate collected (1.45 g.) and recrystallised from alcohol, giving colourless needles, m. p. 104°, not depressed on admixture with 3-nitro-1:5-di-(*n*-butylsulphonyl)-3-ethylpentane. Interaction of an aqueous solution of the sodium salt of *n*-butyl 3-nitroamyl sulphone with bromine at 10–15° gave *n*-butyl 3-bromo-3-nitroamyl sulphone, colourless crystals from alcohol, m. p. 55° (Found: S, 9.95; Br, 25.1. $C_9H_{19}O_4NBrS$ requires S, 10.1; Br, 25.3%).

***n*-Butyl 3-Ketoamyl Sulphone (III; R = Et).**—An aqueous solution of the potassium salt of *n*-butyl 3-nitroamyl sulphone, prepared from 1-nitropropane (4.5 g.) and *n*-butyl vinyl sulphone (7.5 g.) as above, was slowly added to a stirred solution of sulphuric acid (6.5 c.c.) in water (30 c.c.) at 10–15°. Stirring was continued for 30 minutes and the precipitate (4.5 g.) was collected, washed with water, and crystallised from alcohol, giving the ketone as colourless needles, m. p. 89° (Found: S, 15.45. $C_9H_{18}O_5S$ requires S, 15.5%). The 2:4-dinitrophenylhydrazones, m. p. 132°, formed yellow needles from alcohol (Found: N, 14.05; S, 7.8. $C_{11}H_{18}O_6N_4S$ requires N, 14.5; S, 8.3%). The ketone was also formed by acidification of the alkaline filtrate obtained in the condensation of 1-nitropropane with 2-chloroethyl *n*-butyl sulphone (see above).

Tris-(2-methylsulphonyl)nitromethane (IV).—Nitromethane (6 g.), methyl vinyl sulphone (34 g.), alcohol (80 c.c.), and aqueous potassium hydroxide (1 c.c. of 33%) were refluxed for 6 hours. After cooling, the precipitate (20.6 g.) was collected, washed with alcohol, and crystallised from 2-ethoxyethyl alcohol and from acetic acid, giving colourless crystals of the trisulphone, m. p. 219–220° (Found: N, 3.9; S, 25.0. $C_{10}H_{20}O_6NS_3$ requires N, 3.7; S, 25.3%).

Tris-(2-methylsulphonyl)ethylmethylamine.—The nitro-compound (10 g.) was suspended in water (250 c.c.) and shaken with hydrogen and Raney nickel at 20°/1 atm. until absorption was complete. The mixture was then heated to the boil, filtered from catalyst, and allowed to cool. The amine separated in colourless needles, m. p. 218° (Found: N, 4.15; S, 27.25. $C_{10}H_{22}O_6NS_3$ requires N, 4.0; S, 27.5%).

3-Nitro-1:5-di-*p*-tolylsulphonyl-3-ethylpentane (I; R = Et, R' = *p*-MeC₆H₄).—1-Nitropropane (3 g.), *p*-tolyl vinyl sulphone (10 g.), and aqueous potassium hydroxide (1 c.c. of 33%) in alcohol (40 c.c.) were refluxed for 16 hours, cooled, and the solid sulphone which separated was crystallised from acetone, giving white needles, m. p. 151° (Found: C, 55.6; H, 5.8; N, 3.25. $C_{21}H_{27}O_6NS_2$ requires C, 55.6; H, 6.0; N, 3.1%).

2-Nitro-4-*p*-tolylsulphonyl-2-methylbutane (VI).—2-Nitropropane (6 g.), *p*-tolyl vinyl sulphone (10 g.), alcohol (40 c.c.), and aqueous potassium hydroxide (1 c.c. of 33%) were refluxed for 16 hours. After cooling, the separated solid was collected and crystallised from alcohol, giving white needles of the

sulphone, m. p. 122° (Found: C, 52.95; H, 6.2; N, 4.85. $C_{12}H_{17}O_4NS$ requires C, 53.15; H, 6.25; N, 5.15%).

Methyl 3-Nitro-3-p-bromophenylpropyl Sulphone (V; R = Me).—*p*-Bromophenylnitromethane (6 g.) and methyl vinyl sulphone (8 g.) were dissolved in alcohol (40 c.c.) and a few drops of a 33% aqueous solution of methyltriethylammonium hydroxide were added. After 18 hours at 20°, the precipitate (6 g.) was collected and washed with alcohol. Recrystallisation from alcohol gave colourless needles of the *sulphone*, m. p. 142° (Found: N, 4.45; Br, 25.25; S, 10.1. $C_{10}H_{12}O_4NBrS$ requires N, 4.35; Br, 24.85; S, 9.95%).

isoButyl 3-Nitro-3-p-bromophenylpropyl Sulphone (V; R = $CH_3\cdot CHMe_2$).—*iso*Butyl vinyl sulphone (2.5 g.) was added to a solution of the sodium salt of *p*-bromophenylnitromethane (4.0 g.) in water (40 c.c.) and the mixture was stirred at 50° for 6 hours, cooled, and washed with ether. The aqueous solution was treated with acetic acid (2 c.c.), and the separated oil, which solidified on standing, was collected and washed with alcohol. The crude product (2.0 g.) was repeatedly crystallised from alcohol, giving the *sulphone* as colourless needles, m. p. 92° (Found: N, 4.3; Br, 22.2; S, 9.2. $C_{13}H_{18}O_4NBrS$ requires N, 3.85; Br, 22.0; S, 8.8%).

3 : 3'-Dinitro-3 : 3'-dimethyldibutyl Sulphone (IX).—Aqueous potassium hydroxide (1 c.c. of 33%) was added to a solution of 2-nitropropane (8.9 g.) and divinyl sulphone (5.9 g.) in alcohol (40 c.c.). The solution was refluxed for 3 hours, cooled, and the precipitate (7.85 g.) collected and recrystallised from alcohol, giving the *sulphone* as colourless leaflets, m. p. 135° (Found: N, 9.45; S, 10.55. $C_{10}H_{20}O_4N_2S$ requires N, 9.45; S, 10.85%).

3 : 3'-Diamino-3 : 3'-dimethyldibutyl Sulphone.—*3 : 3'-Dinitro-3 : 3'-dimethyldibutyl sulphone* (7.8 g.), suspended in 2-ethoxyethyl alcohol (100 c.c.), was shaken with Raney nickel and hydrogen at 20°/1 atm. until absorption was complete. The filtered solution was concentrated under reduced pressure, and the residue, a viscous semi-solid mass, was dissolved in water, acidified with hydrochloric acid and evaporated to dryness. After extraction with acetone, the *hydrochloride* remained as a white powder (7.2 g.), m. p. 252–255° (Found: N, 8.9; S, 10.3; Cl, 23.0. $C_{10}H_{24}O_2N_2S\cdot 2HCl$ requires N, 9.05; S, 10.35; Cl, 23.0%).

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[Received January 23rd, 1947.]

297. Aliphatic Nitro-compounds. Part XVIII. Interaction of Ketones and Nitro-paraffins.

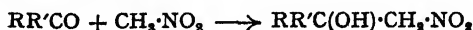
By A. LAMBERT and A. LOWE.

Interaction of acetone and nitromethane in presence of sodium methoxide, sodium hydroxide, quaternary ammonium hydroxides, or triethylamine gives chiefly nitro-*tert*.-butyl alcohol; with secondary amines as catalysts, 1 : 3-dinitro-2 : 2-dimethylpropane is the main product, and this is formed from both nitro-*tert*.-butyl alcohol and 1-nitro-2-methylprop-1-ene with nitromethane. The products obtained from other nitro-paraffins and other ketones are briefly discussed and a reaction mechanism is proposed.

THE literature on the products formed by interaction of ketones and nitro-paraffins, though not extensive, is extremely confusing. According to Fraser and Kon (*J.*, 1934, 604), condensation of acetone and some homologous ketones with nitromethane in the presence of sodium ethoxide, piperidine, pyridine, methylamine, or molecular sodium gives 1 : 3-dinitro-paraffins of the type $RR'C(CH_2\cdot NO_2)_2$ in 15–25% yield. Nitromethane and cyclohexanone with piperidine as a catalyst give 1-nitromethylcyclohexene and a little 1-nitromethylcyclohexanol, and the latter becomes the main product if sodium ethoxide is used as condensing agent. Since completion of the present work, Hass and co-workers (U.S.P. 2,343,256; 2,383,603; cf. *Chem. Reviews*, 1943, 32, 383; *Ind. Eng. Chem.*, 1943, 35, 115) have described improved yields of 1 : 3-dinitro-paraffins from nitromethane and aliphatic or alicyclic ketones by using aliphatic amines as catalysts. They also report failure to duplicate Fraser and Kon's work, saying (U.S.P. 2,343,256) "this disclosure is inoperative and does not enable one skilled in the art to obtain the compounds described".

In addition to the dinitro-paraffins, Hass also obtains from acetone and nitromethane some 1-nitro-2 : 2-dimethylpentan-4-one in yields which vary with the relative proportions of the reactants; with methyl ethyl ketone, some 1-nitro-2-ethylbut-2-ene is produced.

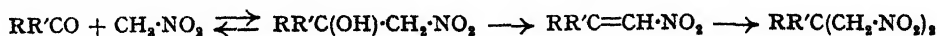
We have now found that, with sodium methoxide as catalyst, nitromethane and aliphatic ketones give only nitro-tertiary alcohols.



e.g., acetone and nitromethane gave nitro-*tert*.-butyl alcohol in 62% yield. Similar results were obtained with sodium hydroxide, quaternary ammonium hydroxides, or triethylamine as catalyst. However, by using secondary amines (diethylamine or piperidine), 68% of

1 : 3-dinitro-2 : 2-dimethylpropane was formed, but with *n*-amylamine the main product was again nitro-*tert*.-butyl alcohol.

Nitromethane and methyl ethyl ketone in the presence of piperidine have given a mixture of 1-nitro-2-methylbut-1-ene, 1-nitro-2-methylbutan-2-ol, and 2 : 2-di(nitromethyl)butane. The isolation of these compounds from one experiment, together with the formation of 1 : 3-dinitro-2 : 2-dimethylpropane from both nitro-*tert*.-butyl alcohol and 1-nitro-2-methylprop-1-ene with nitromethane, indicates that the reaction proceeds as follows :



Hass *et al.* (*loc. cit.*) put forward this mechanism but were unable to isolate any nitro-tertiary alcohol. It is unlikely that 1-nitro-2-diethylamino-2-methylpropane (formed from diethylamine and the nitro-olefin; see this series, Part VII) is an important intermediate product, since on reaction with nitromethane this substance gives only small yields of 1 : 3-dinitro-2 : 2-dimethylpropane.

When cyclohexanone and nitromethane were brought into reaction in the presence of diethylamine, 1-nitromethylcyclohexane, 1-nitromethylcyclohexanol and a small amount of 1 : 1-di(nitromethyl)cyclohexane were formed (*cf.* Fraser and Kon, *loc. cit.*), together with an unidentified product, m. p. 270–271° (acetyl derivative, m. p. 128–129°). The analyses of these agreed with an empirical formula, $\text{C}_{14}\text{H}_{20}\text{O}_3\text{N}_2$, but the apparent molecular weight varied with the method used for the determination.

EXPERIMENTAL.

Nitro-*tert*.-butyl Alcohol.—A mixture of sodium methoxide solution [from sodium (2 g.) and methyl alcohol (50 c.c.)], nitromethane (122 g.), and acetone (600 c.c.) was stirred for 3 days at 20°. After neutralisation (10*N*-hydrochloric acid) and filtration from salt, fractionation gave unchanged nitromethane (62 g.) and nitro-*tert*.-butyl alcohol (71.4 g.) as a colourless oil, b. p. 76–77°/10 mm. (Found : C, 40.7; H, 7.5; N, 11.85. $\text{C}_4\text{H}_9\text{O}_2\text{N}$ requires C, 40.3; H, 7.55; N, 11.75%). Nitro-*tert*.-butyl acetate, prepared from the alcohol by boiling it with acetic anhydride, is a colourless liquid, b. p. 86–88°/13 mm. (Found : N, 8.75. $\text{C}_6\text{H}_{11}\text{O}_4\text{N}$ requires N, 8.7%).

1-Nitro-2-methylprop-1-ene.—Nitro-*tert*.-butyl acetate (7.7 g.) was heated with sodium acetate (0.035 g.) at 110° for 30 minutes, and the mixture then distilled under reduced pressure. The distillate, b. p. 45–65°/12 mm., was diluted with ether, washed with water, dried, and fractionated, giving 1-nitro-2-methylprop-1-ene (4 g.) as a pale yellow liquid, b. p. 54–56°/11 mm. (*cf.* Levy and Scaife, *in the press*).

1 : 3-Dinitro-2 : 2-dimethylpropane.—(a) *From acetone and nitromethane.* A mixture of nitromethane (61 g.), acetone (58 g.), and diethylamine (21.5 g.) was kept at 20° for 28 days, poured into water, acidified (2*N*-hydrochloric acid), and extracted with chloroform. Fractionation of the dried extract gave 1 : 3-dinitro-2 : 2-dimethylpropane (55.5 g.) as an almost colourless liquid, b. p. 130–132°/10 mm., rapidly solidifying to an amorphous mass, m. p. 75–80° (Found : C, 37.2; H, 6.3; N, 17.5. $\text{C}_8\text{H}_{10}\text{O}_4\text{N}_2$ requires C, 37.0; H, 6.2; N, 17.3%).

The same substance was obtained in equal yield using piperidine in place of diethylamine; with *n*-amylamine as catalyst, only 2.5% of the dinitro-compound was formed, together with 10% of nitro-*tert*.-butyl alcohol.

(b) *From nitro-tert.-butyl alcohol and nitromethane.* A mixture of nitro-*tert*.-butyl alcohol (38 g.), nitromethane (20 g.), and piperidine (3 g.) was kept at 20° for 14 days. After working up in the usual way, nitro-*tert*.-butyl alcohol (2 g.) and 1 : 3-dinitro-2 : 2-dimethylpropane (19.8 g.) were obtained. Use of *n*-amylamine in place of piperidine reduced the yield of dinitro-paraffin to 8.2 g., 20 g. of the nitro-alcohol being recovered unchanged.

(c) *From nitro-tert.-butyl alcohol.* A mixture of nitro-*tert*.-butyl alcohol (24 g.) and diethylamine (20 g.) was kept at 20° for 6 days. After acidification (2*N*-hydrochloric acid), the mixture was extracted with ether and the extract fractionated, giving 1-nitro-2-methylprop-1-ene (2 g.), b. p. 54–56°/11 mm., nitro-*tert*.-butyl alcohol (3.4 g.), b. p. 75–76°/10 mm., and 1 : 3-dinitro-2 : 2-dimethylpropane (8.6 g.), b. p. 130–132°/10 mm.

(d) *From 1-nitro-2-methylprop-1-ene and nitromethane.* A mixture of 1-nitro-2-methylprop-1-ene (20 g.), nitromethane (12 g.), and diethylamine (3 g.), after 14 days at 20° and working up in the usual way, yielded unchanged nitro-olefin (7.8 g.) and 1 : 3-dinitro-2 : 2-dimethylpropane (6 g.), b. p. 130–132°/10 mm.

(e) *From 1-nitro-2-diethylaminoisobutane and nitromethane.* The nitro-amine was prepared by interaction of 1-nitro-2-methylprop-1-ene (5.05 g.) and diethylamine (3.7 g.) in dry ether (15 c.c.) at 0° for 1 hour. Evaporation of the ether gave an almost completely crystalline mass of 1-nitro-2-diethylaminoisobutane, which separated from ether on strong cooling as yellow needles, m. p. 76°. Yield, 48%. The nitro-amine decomposed rapidly on keeping and could not be analysed.

A mixture of the nitro-amine (14 g.) and nitromethane (6 g.) in ether (15 c.c.) was kept at 20° for 15 days. The yellow nitro-amine dissolved after 24 hours and the smell of diethylamine became apparent. After acidification, extraction with ether, and distillation, 1 : 3-dinitro-2 : 2-dimethylpropane (1.8 g.), b. p. 130–132°/10 mm., was obtained.

(f) *From nitro-tert.-butyl acetate and nitromethane.* A mixture of nitro-*tert*.-butyl acetate (14 g.), nitromethane (6 c.c.), and piperidine (2 c.c.) was kept at 20° for 16 days and worked up in the usual way. 1 : 3-Dinitro-2 : 2-dimethylpropane (5.1 g.), b. p. 134–135°/10 mm., was obtained.

1-Nitro-2-methylbutan-2-ol.—A mixture of nitromethane (61 g.), methyl ethyl ketone (150 c.c.), and

methyltriethylammonium hydroxide (3 c.c. of 40% aqueous solution) was kept at 20° for 5 days. The mixture was acidified (10*N*-hydrochloric acid) and distilled; nitromethane (45 g.) was recovered, followed by 1-nitro-2-methylbutan-2-ol (12 g.) as a colourless oil, b. p. 96–97°/18 mm. (Found: C, 44.8; H, 8.0; N, 10.8. $C_6H_{11}O_2N$ requires C, 45.1; H, 8.3; N, 10.5%).

1-Nitro-2-methylbut-1-ene.—(a) From methyl ethyl ketone and nitromethane. A mixture of nitromethane (100 c.c.), methyl ethyl ketone (100 c.c.), and piperidine (8 c.c.) was kept at 20° for 9 days. The solution was acidified (2*N*-hydrochloric acid), extracted with ether, and the extract, after being washed successively with dilute sodium hydrogen carbonate and water, was dried and fractionated, giving 1-nitro-2-methylbut-1-ene (7 g.), b. p. 62°/11 mm. (Found: C, 52.3; H, 7.55; N, 12.2. $C_6H_9O_2N$ requires C, 52.2; H, 7.8; N, 12.2%), 1-nitro-2-methylbutan-2-ol (4.4 g.), b. p. 90–91°/11 mm., and 2:2-di(nitromethyl)butane (11.4 g.), b. p. 92°/0.05 mm. (Fraser and Kon, *loc. cit.*, give b. p. 135–138°/9 mm.).

(b) From 1-nitro-2-methylbutan-2-ol and nitromethane. A mixture of 1-nitro-2-methylbutan-2-ol (13.3 g.), nitromethane (6.1 g.), and piperidine (3 c.c.) was kept at 20° for 14 days and worked up in the usual way. 2:2-Di(nitromethyl)butane (12.7 g.), b. p. 106–108°/1 mm., was obtained.

3-Nitro-2-methylbutan-2-ol.—A solution of sodium methoxide [from sodium (3 g.) and methyl alcohol (60 c.c.)] was mixed with nitroethane (225 g.) and acetone (935 c.c.) and the mixture stirred at 20° for 5 days. After acidification (10*N*-hydrochloric acid), filtration from salt and fractionation, nitroethane (170 g.) was recovered and 3-nitro-2-methylbutan-2-ol (51 g.) was obtained as a colourless oil, b. p. 85–86°/14 mm. (Found: C, 45.4; H, 8.0; N, 10.7. $C_6H_{11}O_3N$ requires C, 45.1; H, 8.3; N, 10.5%).

1:3-Dinitro-2:2-dimethylbutane.—A mixture of nitro-*tert*-butyl alcohol (60 g.), nitroethane (32.5 g.) and piperidine (10 c.c.) was kept at room temperature for 3 months. After neutralisation and fractionation, 1:3-dinitro-2:2-dimethylbutane (1 g.), b. p. 128–132°/9 mm., was obtained (Found: N, 15.9. $C_8H_{15}O_4N_2$ requires N, 15.9%).

1:1-Di(nitromethyl)cyclohexane.—(a) From cyclohexanone and nitromethane. A mixture of cyclohexanone (50 c.c.), nitromethane (30 c.c.), and diethylamine (35 c.c.) was refluxed for 10 hours. The solution was acidified (2*N*-hydrochloric acid) and extracted with ether. A colourless solid (12 g.) separated at this point, and was collected and crystallised from 2-ethoxyethyl alcohol, giving colourless prisms of a substance, m. p. 270–271° [Found: C, 63.9; H, 7.3; N, 10.8; *M* (by X-ray determination), 259. $C_{14}H_{20}O_2N_2$ requires C, 63.9; H, 7.2; N, 10.65%; *M*, 263]; the acetate had m. p. 128–129° [Found: C, 61.5; H, 6.8; N, 8.05; *M* (by X-ray determination), 347. $C_{18}H_{24}O_4N_2$ requires C, 62.0; H, 6.9; N, 8.05%; *M*, 348]. The constitution of this substance is unknown.

Fractionation of the ethereal solution gave 1-nitromethylcyclohexene, 1-nitromethylcyclohexanol, and 1:1-di(nitromethyl)cyclohexane (3 g.) as a colourless oil, b. p. 105°/0.1 mm., n_D^{20} 1.4963 (Found: N, 14.2. $C_8H_{14}O_2N_2$ requires N, 13.9%).

(b) From nitromethylcyclohexanol and nitromethane. 1-Nitromethylcyclohexanol (30 g.; Fraser and Kon, *loc. cit.*), nitromethane (15 c.c.), and diethylamine (5 c.c.) were refluxed for 12 hours. After acidification and extraction with ether [some solid, m. p. 270–271° (1.9 g.), separated here; see above], fractionation of the dried extract afforded 1:1-di(nitromethyl)cyclohexane, b. p. 110°/0.2 mm. (Found: N, 13.6%).

3-Amino-2-methylbutan-2-ol.—3-Nitro-2-methylbutan-2-ol (48 g.) in methyl alcohol (900 c.c.) was hydrogenated using Raney nickel at 20°/85 atms. (initial pressure). Fractionation of the filtered solution afforded 3-amino-2-methylbutan-2-ol as a colourless oil, b. p. 65–67°/17 mm. (Found: C, 58.6; H, 12.35; N, 13.9. $C_6H_{11}ON$ requires C, 58.2; H, 12.7; N, 13.6%).

1:3-Diamino-2:2-dimethylpropane.—Hydrogenation of 1:3-dinitro-2:2-dimethylpropane (25 g.) in methyl alcohol (500 c.c.) with Raney nickel (10 g.) at 20°/42 atms. (initial pressure) gave an oil, b. p. 146–156°, which on redistillation from solid potassium hydroxide yielded 1:3-diamino-2:2-dimethylpropane (11.2 g.) as a colourless oil, b. p. 154–156° (Found: C, 58.4; H, 13.6; N, 27.0. Calc. for $C_6H_{11}N_2$: C, 58.8; H, 13.7; N, 27.4%). The dihydrochloride formed prisms from alcohol, m. p. 259°; the dibenzoyl derivative, leaflets from aqueous methyl alcohol, m. p. 152° alone and in admixture with an authentic specimen prepared according to Part XII of this series.

1:1-Di(aminomethyl)cyclohexane.—Reduction of 1:1-di(nitromethyl)cyclohexane (5.5 g.) as described above gave 1:1-di(aminomethyl)cyclohexane (2.6 g.) as a colourless liquid, b. p. 106–108°/10 mm. (Found: C, 67.5; H, 12.3. $C_8H_{18}N_2$ requires C, 67.6; H, 12.7%). The dibenzoyl derivative had m. p. 210° (Found: C, 75.3; H, 7.5; N, 8.0. $C_{22}H_{26}O_2N_2$ requires C, 75.4; H, 7.4; N, 8.0%).

The authors wish to thank Dr. H. A. Piggott and Mr. J. D. Rose for advice and interest in this work.

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[Received, January 23rd, 1947.]

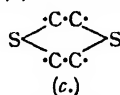
298. The Reaction of Sulphur and Sulphur Compounds with Olefinic Substances. Part I. The Reaction of Sulphur with Mono-olefins and with $\Delta^1:5$ -Diolefins.

By E. HAROLD FARMER and F. W. SHIPLEY.

The nature of the reaction occurring at 140° between sulphur and two classes of olefins has been investigated. Olefins in general give olefin sulphides, $R\cdot S_2\cdot R'$, in which on the average half the original unsaturation is lost and x has values up to 6. In the sulphides from mono-olefins R and R' appear on average to be mono-olefinic and saturated respectively, except that

some redistribution appears to occur in the sulphides from hydroaromatic mono-olefins owing to the facility of occurrence of (probably secondary) dehydrogenation reactions. $\Delta^{1:5}$ -Olefins give in addition to diolefin sulphides, $R \cdot S \cdot R'$, cyclic monosulphides which are formed from only one molecule of olefin. Thus, polyolefins displaying suitably-spaced unsaturation become both inter- and intra-molecularly cross-linked by the sulphur taken into combination. The reaction mechanism is discussed, and it is noteworthy that although substitutive and additive reactions of a radical type play an important role, additive reactions of a polar nature also participate.

THE idea has long been current that sulphur reacts with olefins in an essentially additive manner, although there is no body of evidence in the literature to relate the behaviour of sulphur as a reagent for double bonds with that of any of the numerous common additive reagents. The character of sulphur-olefin reactivity has long been a matter of interest in connexion with the mechanism of vulcanisation of rubbers and of drying oils, but the experiments and speculations of Erdmann (*Annalen*, 1908, 362, 133), Kirchoff (*Kolloid-Z.*, 1913, 13, 49; 1914, 14, 35), Prins (*Chem. Weekblad*, 1917, 14, 932), and many others on this subject have done little to solve the basic problem, as it applies either to high-molecular natural and artificial rubbers or to quite simple olefins such as isobutylene and cyclohexene. Episulphides (thioepoxides) and cyclic disulphides containing respectively the groupings (a) and (b) appear definitely never to have been obtained by the action of sulphur on olefins, and there seems to be no sound evidence to support the view that alternative structures such as (c) and (d) are formed additively at ethylenic centres.



It is necessary, therefore, to find a new basis for formulating the course of reaction of sulphur, and in this connexion attention turns to the behaviour of the closely related element oxygen, which, also, until recently was regarded as functioning normally as a common additive reagent. Sulphur, like oxygen, contains two unpaired electrons in its outer shell, and since it shows no obvious signs in its recorded behaviour of functioning as a polar reagent it may be suspected of resembling oxygen in possessing an inherent tendency to react apolarly. Hence methods which have been successfully used in the investigation of oxygen-reactivity have been applied to the determination of the principles governing sulphur reactions. In conducting the work it has been necessary, as in the comparable oxygen studies, to divide olefins into four classes, *viz.*, (1) mono-olefins, (2) di- and poly-olefins displaying uni-spaced (*i.e.*, 1 : 4-, 1 : 4 : 7-, etc.) unsaturation, (3) di- and poly-olefins displaying bi-spaced (*i.e.*, 1 : 5-, 1 : 5 : 9-, etc., unsaturation) and (4) conjugated di- and poly-olefins, since the detailed course of reaction is greatly influenced by the unsaturation pattern.

The reaction of sulphur with olefinic materials usually becomes appreciable above 100°, and proceeds at a moderate speed at 140°, which is the most usual vulcanisation temperature for rubbers. This, the lowest temperature at which a convenient speed of reaction is obtained, was adopted for our experiments, not merely because of its common use in industrial vulcanisation processes, but also because experience soon showed that operation at substantially higher temperature is attended by serious danger of confusion arising between primary and secondary reactions. A beginning has been made by the investigation of the reaction between sulphur and cyclohexene, this being of special interest, both because this reaction has twice already been examined by previous workers (Jones and Reid, *J. Amer. Chem. Soc.*, 1938, 60, 2452; Meyer and Hohenemser, *Helv. Chim. Acta*, 1935, 18, 1061) with results which are difficult to interpret, and because it brings into consideration whatever relationship there may be between the general or ordinary reactivity of sulphur and the possibly specialised reactivity underlying the Vesterberg procedure for the dehydrogenation of hydroaromatic compounds.

Reaction with cyclohexene.—When cyclohexene is heated with sulphur for several hours in a glass tube or steel autoclave containing air, there is obtained a mixed product composed of sulphurated and unsulphurated materials. The recovered hydrocarbon is wholly unimolecular and contains only a trivial amount of cyclohexadiene and benzene (<1%, determined spectroscopically as benzene), so that simple dehydrogenation of the cyclohexene to a more highly unsaturated state is not an important reaction at 140° (the Vesterberg reaction is usually carried out at 200° and above), unless the cyclohexadiene which is produced is subsequently used up in reaction with sulphur or hydrogen sulphide. The sulphurated products have a very large range of boiling point, but are very sensitive to elevated temperatures, even to those but little higher than the original reaction temperature, so that separation of the products by distillation must be conducted by "molecular" distillation, otherwise progressive (and hitherto unsuspected)

thermal degradation sets in, with formation of moderate yields of alkylthiol, dialkyl sulphide, and hydrogen sulphide. If the distillation temperature is kept below 150° , only the merest traces of hydrogen sulphide and thiol are formed, and the main bulk of material is easily separable with tolerable sharpness into a series of polysulphides $R\cdot S\cdot R'$, $R\cdot S_2\cdot R'$, $R\cdot S_3\cdot R'$, and $R\cdot S_4\cdot R'$. These are the invariable products of reaction under the stated conditions, but they can be progressively broken down at will by being heated for long periods at higher temperatures, and there is no doubt at all that the thiol, hydrogen sulphide, and possibly much of the monosulphide reported by the previous workers, are degradation products, and therefore only *secondary* products, of the olefin-sulphur reaction. The pentasulphide $R\cdot S_5\cdot R'$ derived from *cyclohexene* stands at about the limit of practical distillability for non-rotary molecular stills operating at 10^{-5} – 10^{-6} mm. pressure and temperatures below 150° ; therefore its separation from the higher-boiling residue tended always to be very incomplete, and, in consequence, the total bulk too small to permit of its satisfactory rectification. It is perhaps significant that the undistilled residue before removal of any pentasulphide had an average composition agreeing almost exactly with that required for the hexasulphide. Variation in the proportion of sulphur employed within the observed limits of $\frac{1}{3}$ to $\frac{2}{3}$ atom of sulphur per mol. of olefin affects mainly the yield, and not the nature of the sulphides obtained.

It was at once noticeable that the alkyl radicals in these polysulphides were not wholly saturated, and, indeed, the hydrogen contents of the sulphides as determined by the most careful technique of elementary analysis available usually lay but a little above * those required for the formula $C_6H_9\cdot S_x\cdot C_6H_{11}$, or alternatively those required for an equimolecular mixture of $C_6H_9\cdot S_x\cdot C_6H_9$ and $C_6H_{11}\cdot S_x\cdot C_6H_{11}$ together with (possibly) some small or large proportion of admixed $C_6H_9\cdot S_x\cdot C_6H_{11}$. In other words *the atom-ratio of hydrogen to carbon (H/C) in all the sulphides produced (in the primary reaction) by sulphuration was found to be identical, within the limits of analytical error, with that of the original olefin, which signified that no serious net gain or loss of hydrogen as hydrogen sulphide or thiol could have occurred to that portion of the hydrocarbon which became successfully converted into sulphides*, and hence meant that any postulation of dehydrogenation of the hydrocarbon to give hydrogen sulphide as the first necessary stage of sulphur attack must require as a corollary the complete re-addition of the hydrogen sulphide to the olefinic materials present, and must correspondingly preclude any *overall* hydrogen-enrichment of the sulphurated products at the expense of concomitantly stripped hydrocarbon molecules, but not necessarily the enrichment of individual sulphurated species (disulphides, trisulphides, etc.) at the expense of each other.

The accurate determination of total unsaturation in the partly olefinic sulphides presents a difficult practical problem which has not been satisfactorily solved: catalytic hydrogenation methods fail owing to catalyst poisoning, and all halogen addition methods which we have sought to use are invalidated owing to the high co-ordinating capacity for halogens of the combined sulphur atoms.† The determination of the distribution of unsaturation presents a still more difficult problem. At first, owing to definite analytical indications (derived from the magnitude of the hydrogen contents) that the unsaturation of the polysulphides varied appreciably within the same individual species (*i.e.*, from one sub-fraction to another), and also to the fact that a quite considerable proportion of pure saturated *dicyclohexyl* sulphide could be isolated in the form of its methiodide from the monosulphide derived from *cyclohexene*, it seemed likely that each species of sulphide (mono-, di-, etc.) contained some saturated material, $R_{sat}\cdot S_x\cdot R_{sat}$, and some dialkenyl material, $R_{\overline{1}}\cdot S_x\cdot R_{\overline{1}}$ —these in equimolecular proportions—probably in addition to the “average compound” $R_{sat}\cdot S_x\cdot R_{\overline{1}}$. This generalisation is probably true in respect of the sulphuration products derived from most mono-olefins, but it does not appear to be true of the sulphurated products from hydroaromatic mono-olefins because in such examples a subsidiary phenomenon seems to enter to complicate the normal course of reaction. Infra-red spectroscopic evidence ‡ shows that much of the unsaturation surviving in the sulphides from *cyclohexene* is conjugated unsaturation, and the most likely source of this conjugation (in view of its complete absence from the synthetically derived sulphides of all olefins and polyolefins so far examined) § is dehydrogenation, doubtless produced by secondary

* This excess doubtless merely reflects the usual tendency of hydrogen values to be rather high.

† Some progress in respect of halogen-addition methods has been made by Bloomfield (*cf. J. Soc. Chem. Ind.*, 1945, 64, 274) since this work was carried out.

‡ We record our great indebtedness to Dr. G. B. M. Sutherland and Mr. N. Sheppard for their invaluable co-operation in the determination of the structure of sulphur compounds. All items of infra-red spectroscopic evidence herein depend on their observations.

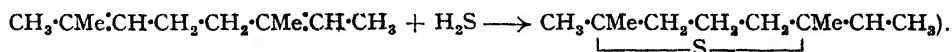
§ The possibility that resonance in groups of vinyl sulphide type ($\cdot C\equiv C\cdot S\cdot$) is in some degree responsible has not yet been specifically examined.

reaction. There is every reason to suspect that the superior ease of dehydrogenation of *cyclohexene* over *cyclohexane* is due to the susceptibility of the α -methylenic hydrogen atoms to removal (as atoms) by the reagent, permitting the *cyclohexenyl* radicals so formed to achieve stabilisation by disproportionation ($2C_6H_9 \cdot \rightarrow C_6H_8 + C_6H_{10}$), or by donation of a second hydrogen atom to sulphur or to $\cdot SH$ radicals; there is no obvious reason why the *cyclohexenyl* groups of sulphides $R \cdot S_x \cdot R'$ should be immune from similar dehydrogenation, but of course to the extent that the unsaturation of some of the groups R and R' is increased, that of others must ultimately disappear, so that the overall (or average) unsaturation is not quantitatively altered. There are no experimental indications that any considerable amount of free hydrogen sulphide (rather than $\cdot SH$ or $\cdot S_2H$) is ever produced by dehydrogenation reactions and therefore used up again in additive reactions, although minor reactivity of this type is not unlikely.

Reaction with 1-Methylcyclohexene.—The reaction followed exactly similar lines to that observed for *cyclohexene*. Only a trace of free hydrogen sulphide and no thiol was formed; also the amount of monosulphide, $R \cdot S \cdot R'$, produced was very small. That portion of the product which was distillable under high vacuum below 150° consisted of mono-, di-, tetra-, and penta-sulphides, the last being distillable only with great difficulty and hence not completely isolable from the high-boiling residue, or wholly separable from admixture with the tetra-sulphide. The sulphides again agreed in composition with the general formula $R \cdot S_x \cdot R'$, the groups RR' containing between them, on average, one double bond. Probably conjugation due to dehydrogenation appears in these sulphides (although this has not been experimentally verified), so precluding them from representation by the average formula $C_7H_{11} \cdot S_x \cdot C_7H_{13}$ or by the equivalent mixture of saturated and diolefinic forms $C_7H_{13} \cdot S_x \cdot C_7H_{13}$ and $C_7H_{11} \cdot S_x \cdot C_7H_{11}$.

Reaction with isoButylene.—In this instance also there was no appreciable amount of hydrogen sulphide or thiol produced, and the lowest sulphide isolated was $R \cdot S_2 \cdot R'$. This, together with the tri- and tetra-sulphide, formed almost the whole reaction product. No conjugation of the groups R and R' was observed in this case.

Reaction with Diolefins.—The manner of reaction of two bi-spaced olefins of the terpene group, *viz.*, dihydromyrcene, $CH_3 \cdot CMe \cdot CH \cdot CH_2 \cdot CH_2 \cdot CMe \cdot CH \cdot CH_3$, and geraniolene, $CH_3 \cdot CMe \cdot CH \cdot CH_3 \cdot CH_2 \cdot CMe \cdot CH_2$ was next examined, the thermal treatment being conducted as before. With dihydromyrcene about two-thirds of the hydrocarbon was recovered in un-sulphurated condition. Of the sulphurated products about half consisted of a mobile *mono-sulphide* $C_{10}H_{18}S$, which from its low boiling point, its not unpleasant smell, the zero value of its active hydrogen content, and the total absence of thiol reactivity, was clearly a cyclic sulphide. The remaining half was a red, viscous oil, easily decomposable, when heated above 140° or very slowly at 140° when no solvent or excess hydrocarbon was present; this product was wholly undistillable except at 10^{-5} – 10^{-6} mm. in a molecular still, and apparently consisted of mixtures of sulphides of the type $R \cdot S_x \cdot R'$ analogous to these described above. The mono-sulphide readily formed a crystalline sulphonium iodide with methyl iodide and had a H/C ratio indistinguishable from that of the parent dihydromyrcene. The latter characteristic ruled out the possibility that hydrogen sulphide formed by dehydrogenation of some of the hydrocarbon molecules had added to the double bonds of other molecules to give a *saturated* cyclic product (*e.g.*,



Indeed, observation of the infra-red spectrum showed unmistakably that the monosulphide was unsaturated, and also revealed the presence of certain characteristic olefinic groupings (see below).

Geraniolene behaved in a precisely similar manner with sulphur at 140° , the sulphurated product containing a large proportion of olefinic cyclic sulphide $C_9H_{16}S$ and a residue of mixed sulphides which appeared to be of type $R \cdot S_x \cdot R'$.

Formulation of the Sulphides. Open-chain Sulphides.—The method of linking of the sulphides derived from *cyclohexene*, 1-methylcyclohexene, and *isobutylene* was first examined by desulphuration. The removal of sulphur by hydrogenolysis from open-chain forms $R \cdot S_x \cdot R'$ should give simple saturated hydrocarbons RH , $R'H$ (RH_2 or $R'H_2$ if R or R' is olefinic),

whereas its removal from forms such as $S < \begin{array}{c} \text{C} - \text{C} \\ | \quad | \\ \text{C} - \text{C} \end{array}$, showing carbon-to-carbon cross-linking,

would inevitably give hydrogenated hydrocarbon dimers $R-R$ (or $RH_2 \cdot R$, $RH_2 \cdot RH_2$, etc., if the sulphide is olefinic). Bougault and his co-workers had shown that sulphur can be entirely

removed from a wide range of sulphur compounds by acting on them with Raney nickel containing adsorbed hydrogen; Mozingo (*J. Amer. Chem. Soc.*, 1943, **65**, 1013) had later shown that the action in the case of typical organic sulphides consisted in the severing of the C-S bonds with formation of the corresponding simple hydrocarbons: $R \cdot S \cdot R' \xrightarrow{2H_2} RH + R'H + H_2S$.

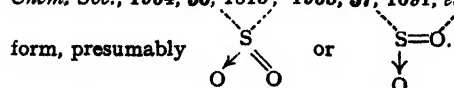
The procedure was applied to the total sulphur product from cyclohexene, 1-methylcyclohexene, and isobutylene, and also to homogeneous monosulphides such as dicyclohexyl and dicyclohexenyl sulphides. In each case there remained volatile (unimolecular) hydrocarbons free from corresponding dimeric (carbon-to-carbon cross-linked) forms.

It appears, therefore, that sulphur molecules (probably chains of sulphur atoms derived by rupture of S_x rings) unite at either end with olefin molecules in virtue of the reactivity of their terminal atoms. It may tentatively be considered that such open-chained sulphur molecules will have radical ends.† In the case of the monosulphides (which are formed usually in small yield) there are two possible routes of formation: they may result from the union of single sulphur atoms (presumably $\cdot S \cdot$) with the olefins, or from the degradation of already formed polysulphides or polysulphide radicals, $R \cdot S_x \cdot$, to give $RS \cdot$. Experience has shown that when sulphur is liberated in the course of a thermal decomposition reaction (presumably in atomic condition) it is energetically reactive towards olefins, whereas elementary sulphur reacts quite slowly, even with very reactive olefins such as polyisoprenes. There is some ground, therefore, for suspecting that the small yields of monosulphides ordinarily obtained in cautiously conducted olefin-sulphur reactions may not arise from the action of monatomic sulphur. It is convenient, however, in order to simplify the argument, to assume provisionally in the following section that the reagent is monatomic biradical sulphur.

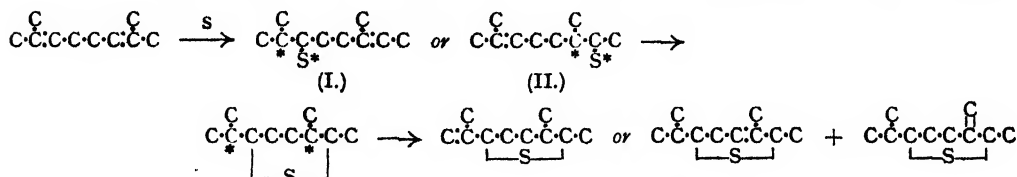
Cyclic Forms.—Owing to (1) the plurality of reaction paths open to the olefin and the sulphur reagent (having regard to the potential versatility of both), and (2) the strong possibility that cyclisation will lead to the formation of both 5- and 6- (but not 3-, 4-, and 7-) membered rings, there is little likelihood that the cyclic products formed respectively from dihydromyrcene and geraniolene will be homogeneous compounds. Efforts to separate pure or tolerably pure isomeric or structurally related forms from the two volatile sulphides—either by direct fractionation or by the formation of crystalline derivatives—proved abortive. The probability of their structural heterogeneity, however, is enhanced by the complexity of their infra-red absorption spectra in comparison with the spectra of authentic specimens of allied 6-membered saturated cyclic sulphides. The absorption curves, indeed, were in each case too complex to reveal directly the precise character of all the compounds, and for the present, necessary comparisons with corresponding 5-membered forms have had to be omitted owing to difficulties attending synthesis of the latter. But although complete interpretation of the data has not yet been possible, the deductions which have been made from a partial analysis (*q.v.*) are illuminating.

It is necessary to envisage that a radical reagent may in general attack an olefin either by replacing an α -methylenic hydrogen atom or by adding to the double bond, and it is not *a priori* impossible for the two types of reaction to occur side by side. The degree of variability to be associated with the α -methylenic (substitutive) type of reaction is mainly, but not solely (see below), that arising from the presence of two or more α -methylenic groups in the olefin undergoing attack, with the resultant possibility that attack may be initiated at more than one point in the olefinic chain. The degree of variability to be associated with the additive reaction is (for a mono-olefin) only that which could arise if the radical reagent possesses the ability to add at either end of the double bond. Now it has already been suggested by one of us (Farmer, *J. Soc. Chem. Ind.*, 1947, **66**, 86) that the addition of radicals and radical reagents to unsymmetrical alkylethylenes is just as strictly and universally governed by a "radical-addition" rule as is the corresponding addition of polar reagents by the well-known "polar-addition" rule of Markovnikov. Thus, whereas Br^- would always add to the alkylated carbon atom in $CHR:CH_2$, $Br \cdot$ (and the same applies also to other radical addenda) could just as inevitably add, if it added at all, to the other carbon atom.

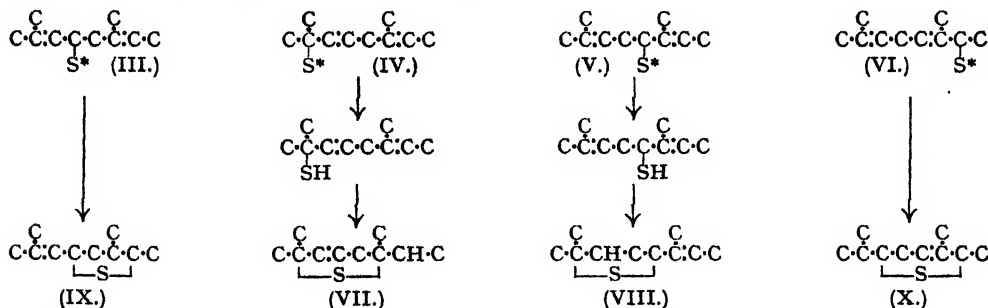
† Molecular oxygen appears to have both a biradical and an unsaturated form ($\cdot \ddot{O} : \ddot{O} \cdot$ and $\ddot{O} = \ddot{O} \cdot$), the latter of which enables it to form interpolymers with some olefins. Sulphur does not appear to form interpolymers at all and hence presumably has no unsaturated reaction form, but sulphur dioxide forms interpolymers with great ease (Staudinger and Ritzenthaler, *Ber.*, 1935, **68**, 455; Marvel *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 1815; 1935, **57**, 1891, *et seq.*) and so must be able to assume a bifunctional reaction



The approach to the determination of the structures present, and to the formulation of an adequate reaction scheme, has been greatly facilitated by Naylor's parallel study of the polar and non-polar addition of hydrogen sulphide to di-isoprenic hydrocarbons (see Part II, following paper); for the results of this study are clear-cut, since not only are the cyclic products then saturated, and so free from troublesome non-uniformity in the degree and position of unsaturation, but the unsaturation pattern of the original di-isoprene is exactly that required to give either by the polar or by the non-polar process *solely* 6-membered sulphide rings. In contrast, the additive reaction which a single sulphur atom may be expected to pursue presents the high probability that marked non-homogeneity will arise in the end-product, since the bi-radical adducts (I and II) which are probably first formed, must achieve stabilisation by hydrogen transfer (*i.e.*,



probably mainly by disproportionation) in such a way that on average one double bond (and that bond not usually one of the original two) is retained and one lost; to some doubtless minor extent, however, the disproportionation may well yield an equimolecular mixture of the corresponding diolefinic and fully saturated sulphides.† If, however, reaction follows the α -methylene course, attack by the reagent is likely to be confined almost entirely to the two α -methylene groups between the two double bonds, leaving those in the methyl groups intact; but owing to the capacity for resonance in any radical propene system that is formed when an α -methylene hydrogen atom is detached ($\text{C}^*\text{C}=\text{C} \rightleftharpoons \text{C}=\text{C}\text{C}^*$) there will be four potential ways (III—VI) in which reaction may be initiated but only two of these, *viz.*, (III) and (VI), will lead to the successful production of cyclic forms if the radical-addition rule is to be obeyed and only 5- and 6-membered rings are capable of formation.

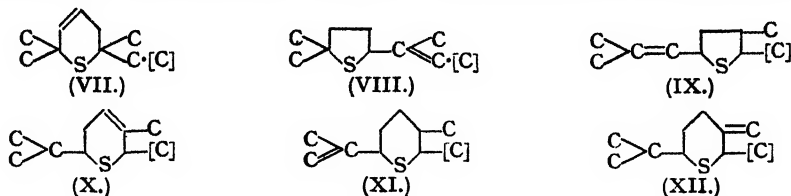


There is, however, a further possibility for the formation of cyclic sulphides which cannot be neglected, *viz.*, that which arises if the active thiol centres in (III—VI) become stabilised by capture of the hydrogen atoms (see preceding footnote) and the resulting $\cdot\text{SH}$ groups thereafter add themselves by polar mechanism (wherever the Markovnikov rule and the usual limitation of ring size jointly permit) to the more remote double bond. This polar type of addition would be likely to occur readily owing to the strong catalytic action of the free sulphur present (see Part II).‡ Of the four α -methylene sulphuro-forms, however, only two, (IV) and (V), would yield cyclic sulphides (*viz.*, VII and VIII); the olefinic thiols corresponding to (III) and (VI), if formed at all, would survive. Actually, the amount of such thiol that survived as determined

† The path taken by the disproportionation probably depends on the incidence of intra- and inter-molecular hydrogen displacements respectively, the former leading exclusively to the product of average unsaturation (*i.e.*, to the mono-olefinic cyclic sulphide) and the latter probably largely to the mixture of saturated and diolefinic forms. To the extent that the addition of the sulphur to one double bond is completed (*i.e.*, the first-formed radical sulphuro-product becomes stabilised by hydrogen rejection *before* that to the other double bond occurs), to that same extent the discarded hydrogen atoms are likely to add to the $\cdot\text{S}^*$ groups giving the thiols corresponding to (III)—(VI).

‡ Since polar and non-polar additions of hydrogen bromide (or hydrogen sulphide) to olefins occur readily side by side, there is no reason to suppose that the two kinds of addition may not occur together in this case.

by usual methods was extremely small, but was possibly slightly underestimated; only later did the very efficient analytical and separative method used in Part II become available. Thus, altogether, the cyclic sulphides likely to be formed from dihydromyrcene by α -methylenic initiation are (VII), (VIII), (IX), and (X); and those from geraniolene precisely the same forms minus the carbo-group (CH_3) enclosed in square brackets. Correspondingly those likely to be formed by additive initiation are (X) and (XI), with possibly a very minor amount of (XII).



Now the infra-red absorption data show that, as regards the 6-membered forms from both dihydromyrcene and geraniolene, the skeletal pattern depicted in (VII) preponderates over that in (X); also it is plain that one or more of the isomers present contains a methyleno-grouping $\text{CH}_2\text{:CRR'}$ such as occurs in (XI) and in the minor isomer (XII). Hence α -methylenic initiation of the sulphuration reaction undoubtedly occurs to an important extent and may well greatly exceed additive initiation. It is of especial interest that the change from the CRR':CHR' structure occurring in the olefinic units of the di-isoprene to the CHR':CHR' structure of the derived cyclic (and doubtless also of the cross-linked) sulphuro-product, as seen in (VII), with all that it implies in the way of α -methylenic initiating attack at a in $\text{CH}_2\text{:CMe:CH-CH}_2$, as discussed above, is encountered again in the sulphuration of rubber, since Sutherland and Sheppard's infra-red spectroscopic data (private communication) show that the progress of this change keeps pace with increase in the uptake of sulphur.

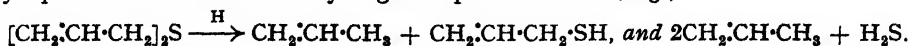
It is to be noted that no products of the episulphide (thioepoxide) type have been discoverable in the fore-runs of the sulphurated mono-olefins or in the cyclic monosulphide fractions from dihydromyrcene and geraniolene; and indeed, no adequately substantiated method of obtaining such compounds save the usual one of reaction between sulphide and suitable halogeno-compounds appears yet to be known. The chemical behaviour of thioepoxycyclohexane, a typical compound of this group, differs considerably from that of the open-chain and cyclic monosulphides discussed above.

Nature of Sulphur Vulcanisation and the Stability of Sulphurated Products.—It has been shown by one of us (Farmer and Michael, J., 1942, 513) that decomposing peroxides effectively promote the carbon-to-carbon cross-linking (α -methylenically initiated) of olefinic materials, and also of ketonic and carboxylated materials (cf. Farmer, "Advances in Colloid Science," 1946, II, 316). Decomposing diazo-compounds often have a similar effect, and with both classes of reagent the process follows a radical mechanism which is irreversible except in so far as the cross-linked products become broken down (and even then not usually into their exact precursors) when they are heated to the point of thermal breakdown of the weakest C-C bonds ($>250^\circ$). With regard to sulphur vulcanisation, the only cross-linking which has been discoverable in the present investigation is that brought about by the linking of the hydrocarbon chains through sulphur atoms or groups of sulphur atoms. The concomitant formation of monosulphide rings in the case of di-isoprenes is to be regarded as amounting to *intramolecular* cross-linking, the different olefinic units becoming joined being in the same instead of in different molecules; such intramolecular linking is of course liable to take place wherever the reactant olefin molecules contain two or more suitably-spaced double bonds. But to the extent that cyclising sulphuration occurs at the expense of true cross-linking, the ingoing sulphur is apparently not used effectively (or at least not in the most effective way) for the conferring of "vulcanised" properties. The sulphur-vulcanisates, as a class, whether formed from short-chained olefins or high-molecular polyolefins, differ greatly from the carbon-to-carbon cross-linked vulcanisates in being highly susceptible to thermal treatment at temperatures but little above (or, possibly, where heating is very unduly prolonged, even at) the vulcanisation temperature. This relative instability (thermolability) appears to be a property of considerable moment in connection with the technology of natural and synthetic rubbers, causing as it does the replacement of some primary structures by secondary ones. The two structural features concerned in this instability are the C-S bonds and (in the case of polysulphides) the polysulphide chains.

The Stability of C-S Bonds.—The susceptibility of C-S bonds to thermal degradation is

reserved for future study. In general, the strength of the bonds as it occurs in cross-linked structures is likely to vary very appreciably with the nature of the hydrocarbon chains in the immediate vicinity of the bond: indeed, having regard to the foregoing results, distinction may be made between three types of monosulphide bridge, *viz.*, (a) the diallylic type, $\text{C}=\text{C}-\text{C}-\text{S}-\text{C}=\text{C}$, (b) the alkyl-allyl type $\text{C}-\text{C}-\text{C}-\text{S}-\text{C}=\text{C}$, and (c) the dialkyl type, $\text{C}-\text{C}-\text{C}-\text{S}-\text{C}-\text{C}$. As regards the stability of the C-S bond to chemical reagents, it has previously been suggested by one of us that the well-known non-uniform action of organic bases on the sulphur vulcanisates of rubber is probably connected with differences in structure near the sulphur bridge; in the present paper, however, attention is confined to evidence concerning the breaking of C-S bonds (a) under the reducing action of sodium in alcohol, and (b) by action of methyl iodide.

Experiment showed that completely saturated sulphides such as di-*n*-propyl sulphide and di-*n*-butyl sulphide remained unattacked by the reducing agent, whereas dialkenyl sulphides such as diallyl, dicrotyl, and dicyclohex-2-enyl sulphides broke down readily to give approximately equimolecular amounts of hydrogen sulphide and thiol, *e.g.*,



Mixed sulphides, of which two (*propyl allyl sulphide* and *cyclohexyl cyclohexenyl sulphide*) were tested, gave an intermediate result, passing to the corresponding thiol but giving no hydrogen sulphide. Thus the C-S bond seems to be attacked by the reducing agent only when the carbon atom is in the α -position to a double bond, or in other words the sulphur atom can be reductively detached from α -methylene groups to which it is linked, but not from saturated carbon chains. The cyclic sulphides from dihydromyrcene and geraniolene gave, as would be expected from the constitutions assigned above, much thiol but no hydrogen sulphide, but reaction was considerably more sluggish, presumably on account of the alkyl substitution at each of the α -methylene groups. For comparison, a compound of the olefin thioepoxide group, *viz.*, thioepoxycyclohexane, was tested: this, in spite of the saturated chain attached on either side to the sulphur atom, underwent ready reduction to a mixture of thiol and hydrogen sulphide.

Instability of Polysulphide Chains.—The ability of sulphur atoms to become linked in chains or groups, and for elementary sulphur to exist normally in closed chains of eight, six, or possibly fewer atoms is commonly regarded as an expression of the strong co-ordinating power of sulphur, and hence there is some expectation that branching of sulphur chains due to co-ordination

(*e.g.*, $\begin{array}{c} \text{S}\cdot\text{S}\cdot\text{S}\cdot\text{S}\cdot \\ \downarrow\downarrow \\ \text{S}\quad\text{S} \end{array}$) may frequently occur. The high-molecular polysulphides formed by the polymeric

interaction of organic dihalides and sodium tetrasulphide (Patrick, *Trans. Faraday Soc.*, 1936, 32, 347) are reported to contain co-ordinated sulphur atoms in their polysulphide groups, since a proportion of the sulphur can be easily removed by caustic alkali. It is reasonable to suppose that the alleged co-ordinated structure is derived directly from the tetrasulphide reagent, and that corresponding syntheses starting out from normal-chained polysulpho-reagents will yield unco-ordinated polysulphides which will not be "stripped" by caustic alkali (*cf.* Patrick, *loc. cit.*) or by sodium sulphite (*cf.* Parker, *India Rubber J.*, 1945, 108, 387). A study of polysulphide constitution and instability will appear in a later part of this series; therefore it suffices now to point out that in our experiments the removal of sulphur by caustic alkali or sodium sulphite succeeds with the above-described products of the olefin-sulphur reaction *only* to the extent of a few units %, suggesting that the sulphur chains are almost wholly unbranched; in contrast to this, however, the diethyl tetrasulphide derived from sulphur monochloride, usually believed to be $\text{Cl}\cdot\text{S}\cdot\text{S}\cdot\text{Cl}$, and ethylthiol ($\text{Cl}\cdot\text{S}_2\cdot\text{Cl} + 2\text{Et}\cdot\text{SH} \longrightarrow \text{Et}\cdot\text{S}\cdot\text{S}_2\cdot\text{S}\cdot\text{Et} + 2\text{HCl}$), as also that derived by the interaction of sodium tetrasulphide which according to the foregoing indications is branched, and ethyl iodide, surrenders nearly half its sulphur to the stripping agent. Hence there is no certainty that sulphur removed by mild stripping agents is necessarily co-ordinated sulphur, or that straight sulphur chains cannot often be ruptured and deprived of part of their sulphur by the same means.

All di- and poly-sulphides formed in the olefin-sulphur reaction decompose progressively at temperatures above 140° (especially from 160° upwards) into hydrogen sulphide, thiol, and monosulphide, but when temperatures above 140° are avoided in the working up of the products comparatively little monosulphide (with some olefins, none at all) and only traces of hydrogen sulphide are formed. Therefore the formation of a large proportion of monosulphide in any olefin-sulphur reaction is fairly safely to be attributed to secondary action, *i.e.*, to thermal decomposition of primary polysulphides due to too long heating or too high temperatures; apparently, however, some monosulphide is produced as a primary product, and there is no

evidence as yet to suggest that the cyclic monosulphides from the di-isoprenes are other than primary products, although thermal decomposition of polysulphides may well be able to produce additional amounts. The amount of thiol formed in the thermal decomposition of the polysulphides from cyclohexene (as also those from 1-methylcyclohexene) is comparatively large, being formed apparently by progressive breaking of the S-S-S- chains, followed by capture of hydrogen atoms from surrounding olefinic molecules ($R-S-S-S-SR' \rightarrow R-S^*$ or $R'-S^* \rightarrow R-SH$ or $R'-SH$). Experiment, indeed, showed that when a polysulphide mixture was distilled above the decomposition temperature, the later distillate fractions showed a H/C ratio progressively smaller and smaller until finally a solid residue containing 39.5% of sulphur but only 3.75% of hydrogen (H/C = 6:4.75) was left. The thiol formed by degradation appears always to be partly olefinic. Disproportionation of the sulphur content doubtless normally accompanies thiol formation when the sulphur chain is severed; Hinsberg (*Ber.*, 1910, 43, 1874) early observed that aromatic disulphides yielded monosulphide and trisulphide as well as some thiol; and other similar instances are on record.

The Sulphur Reagent and the Initiation of Reaction.—It is provisionally concluded from the foregoing that the ordinary reaction form of sulphur in the rather slow sulphur-olefin reactions is the open, radical-terminated sulphur chain, and consequently that in the formation of the cyclic monosulphides the first step may still possibly consist in the union of one end of such sulphur chain with an olefin molecule, later to be followed by rupture of the sulphur chain ($>C-S-S-S- \rightarrow >C-S- + -S-S-S-$). The preceding results provide some ground for believing that α -methylene initiating attack by the sulphur reagent predominates over additive attack. A difficulty, however, arises in connexion with the latter view, which is left for future resolution, *viz.*, that there is a very sharp contrast between the relatively facile carbon-to-carbon molecule-linking action of peroxidic oxygen, *i.e.*, of the free radicals such as $\cdot OH$ derived from decomposing peroxides, ($2C_6H_{10} + 2\cdot OH \rightarrow C_6H_9\cdot C_6H_9 + 2H_2O$) and the inefficient, but not unknown, similar cross-linking action of sulphur or sulphuro-radicals. This seems to suggest that the appearance of radical centres on α -methylene carbon atoms either occurs relatively rarely in sulphur-olefin reactions or else such centres do not ordinarily get beyond the influence of the reacting sulphur.

EXPERIMENTAL.

(Analyses are by Dr. W. T. Chambers and Miss H. Rhodes.)

Action of Sulphur on cycloHexene.—cycloHexene (88 g.) and sulphur (25 g.) were heated together in a rotating steel autoclave for *ca.* 5 hours. A portion of the liquid product was shaken repeatedly with cold dilute potassium hydroxide solution, and the combined washings acidified with hydrochloric acid and then extracted with ether. The ethereal extract gave no appreciable residue (a smell only) of thiol on evaporation; therefore the total neutral product after being carefully freed from the unchanged cyclohexene by distillation was directly fractionated. The dark brown viscous liquid was first heated at 0.1 mm. pressure (the heating bath being kept below 140°), whereupon a nearly colourless oil (4 g.), b. p. 70–100°, distilled. This was re-fractionated, giving (i) a monosulphide, b. p. 70° (*ca.* 0.5 g.) and (ii) a disulphide of b. p. 106° (*ca.* 3.4 g.). The monosulphide was a mixture of unsaturated and saturated forms (Found: C, 72.9; H, 10.5; S, 16.4; H:C = 10.2:6. Calc. for $C_{12}H_{20}S$: C, 73.4; H, 10.3; S, 16.35%; H:C = 10:6. Calc. for $C_{12}H_{22}S$: C, 76.65; H, 11.15; S, 16.2%; H:C = 11:6), containing some dicyclohexyl sulphide since it gave with methyl iodide a poor yield of dicyclohexylmethylsulphonium iodide, m. p. 110.5° (mixed m. p. with authentic specimen derived from pure dicyclohexyl sulphide, 110.5°) Meyer and Hohenemser (*loc. cit.*) had shown that less cautious heating of the total sulphuration product gave a much higher yield than that here obtained of a comparable monosulphide which was thought to consist wholly or mainly of dicyclohexyl sulphide, since it gave with methyl iodide the above mentioned sulphonium iodide, m. p. 110.5°. The disulphide, also, was partly unsaturated (Found: C, 63.4; H, 9.05; S, 27.5; H:C = 10.5:6. $C_{12}H_{20}S_2$ requires C, 63.1; H, 8.8; S, 28.05%. $C_{12}H_{22}S_2$ requires C, 62.6; H, 9.65; S, 27.8%).

The viscous residue in the still was transferred to a "molecular" still and further fractionated. In this operation a Waterman (vertical-type) still gave poor results owing to unavoidable "channeling" of the distilland on the heating surface due to low wetting-capacity for glass: hence a pot-still operating at *ca.* 10⁻⁶ mm. was used in preference. Numerous fractions of increasing sulphur content were successively collected, including two fractions both showing unsaturation, consisting respectively of a *tri*- and a *tetra*-sulphide. The trisulphide, $n_D^{18} 1.5884$, was a thick, pale yellow liquid (Found: C, 55.6; H, 7.95; S, 36.4; H:C = 10.2:6. $C_{12}H_{20}S_3$ requires C, 55.3; H, 7.75; S, 36.95%. $C_{12}H_{22}S_3$ requires C, 54.9; H, 8.45; S, 36.65%), and the tetrasulphide, a still more viscous yellow liquid (Found: C, 49.7; H, 6.95; S, 43.15; H:C = 10.0:6. $C_{12}H_{20}S_4$ requires C, 49.3; H, 6.9; S, 43.8%; the latter had $n_D^{18} 1.6130$, $d_4^{25} 1.209$, $[R_L]_D 84.20$ (Calc. for $C_6H_{11}\cdot S_4\cdot C_6H_{11}$, using Twiss's refractivity value for the sulphur of disulphides: 85.15).

The final residue in the still (*ca.* 34 g.) was a very dark, viscous liquid, varying a little in composition from experiment to experiment. Typical analytical values were: C, 40.95; H, 6.75; S, 53.45; H:C = 10.05:6. (Calc. for $C_{12}H_{20}S_5$: C, 40.45; H, 5.65; S, 53.9%). The separation of a pentasulphide from this residue by further distillation could be effected only with difficulty and incompletely. One such crude product, a reddish oil, had S, 52.9% (Calc.: S, 53.9%).

The recovered cyclohexene was examined spectroscopically in U.V. light, by Dr. H. P. Koch. Less than 1% of benzene and an almost negligible amount of cyclohexadiene were found to be present.

Several further reactions between cyclohexene and sulphur were carried out as above, diminishing proportions of sulphur being used (down to 0.18 atom per mol.). The sulphurated products were in all cases quantitatively similar to the foregoing, but the total yield diminished with reduction in the amount of sulphur employed.

Action of Sulphur on 1-Methylcyclohexene.—The hydrocarbon (30 g.) and sulphur (7 g.) were heated in a sealed tube at 140–145° for ca. 6 hrs. The unchanged hydrocarbon (15 g.) was distilled off through a column, leaving a rather thick brown liquid, from a sample of which repeated vigorous agitation with aqueous sodium hydroxide extracted no thiol. Distillation at 0.1 mm. (bath below 145°) gave only a very small amount (too small for refractionation) of crude monosulphide, contaminated with hydrocarbon (Found: S, 12.2. $C_{11}H_{18}S$ requires S, 14.3%). Continuation of the distillation at 10⁻⁶ mm. gave a succession of fractions of increasing viscosity and deepening yellow colour corresponding respectively to disulphide $C_7H_{11}S_2 \cdot C_7H_{13}$ (Found: C, 65.0; H, 9.55; S, 25.3; H:C = 12.25:7. $C_{14}H_{24}S_2$ requires C, 65.6; H, 9.45; S, 25.0%), trisulphide, $C_7H_{11}S_3 \cdot C_7H_{13}$ (Found: C, 57.85; H, 8.4; S, 34.0; H:C = 12.1:7. $C_{14}H_{24}S_3$ requires C, 58.25; H, 8.4; S, 33.35%), and a tetrasulphide, $C_7H_{11}S_4 \cdot C_7H_{13}$ (Found: C, 52.25; H, 7.7; S, 39.85%; H:C = 12.3:7. $C_{14}H_{24}S_4$ requires C, 52.45; H, 7.55; S, 40.0%). The pentasulphide, which distilled with great difficulty, was not completely isolated, or wholly freed from residual tetrasulphide. The crude fraction formed a dark reddish oil (Found: C, 49.6; H, 7.5; S, 43.1. $C_{14}H_{24}S_5$ requires C, 47.6; H, 6.85; S, 43.1%).

Action of Sulphur on isoButylene.—The liquid hydrocarbon (56 g.; 1 g.-mol.) was introduced at -50° into a steel autoclave which contained sulphur (35 g.; 1.1 g.-mol.). The sealed autoclave was heated at 140–150° for 14 hrs., then strongly cooled and opened. A sample of the liquid contents was tested at once for thiol by Bell and Agruss's test (*Ind. Eng. Chem. Anal.*, 1941, 13, 297); no significant proportion was present. The unreacted isobutylene was allowed to evaporate, and the liquid residue (53.8 g.) distilled. The first distillate was a red liquid, b. p. 80°/12 mm. (21.8 g.), and the second a dark red rather thick liquid, b. p. 90°/0.5 mm.; there remained a dark red very viscous liquid in the still (ca. 14 g.). The first two distillates were separately fractionated and the products refractionated. Although these two stages of rectification did not result in perfect segregation of the individual polysulphides, an approximate separation into di-, tri-, and tetra-sulphides was achieved. The various fractions were yellow, reddish yellow, red and dark red liquids of increasing viscosity. The following analytical data for the fractions (a)–(k) were obtained:—

Fraction, b. p./0.5 mm.	Found, %.			n.	H : C.	Sulphide.
	C.	H.	S.			
(a) Forerun						
(b) 38°	54.5	10.0	34.95	n_D^{20} 1.5005	8.75 : 4	Di-
(c) 38–39°	52.95	9.6	37.0	n_D^{20} 1.5070	8.7 : 4	
(d) 39–40°	—	—	—	—	—	—
(e) 40–44°	—	—	44.5	$n_D^{19.5}$ 1.5292	—	—
(f) 44–51°	—	—	44.7	$n_D^{19.5}$ 1.5330	—	—
(g) 51–60°	44.65	8.2	45.4	$n_D^{19.5}$ 1.5407	8.8 : 4	Tri-
(h) 60–70°	43.65	7.65	47.6	$n_D^{19.5}$ 1.5620	8.4 : 4	—
(i) 70–80°	—	—	—	—	—	—
(j) 80–90°	38.95	6.75	53.6	—	8.26 : 4	Tetra-
(k) Viscous residue	41.3	6.55	51.6	—	7.56 : 4	—

($C_8H_{16}S_2$ requires C, 54.5; H, 9.1; S, 36.35%; $C_8H_{16}S_3$ requires C, 46.1; H, 7.7; S, 46.1%; $C_8H_{16}S_4$ requires C, 40.0; H, 6.75; S, 53.3%.)

It is seen that no definite monosulphide fraction could be isolated and that the ultimate very viscous residue (although doubtless very heterogeneous, and probably containing *inter alia* some triolefinic sulphides derived by double cross-linking) approximated in average composition to tetrasulphide.

Action of Sulphur on Dihydromyrcene.—The hydrocarbon (60 g.) and sulphur (6 g.) were heated at 140° for about 5 hours in a steel rotating autoclave in an atmosphere of nitrogen. The product was a dark red, somewhat viscous liquid, from which unused hydrocarbon (ca. 41 g.) was distilled through a fractionating column at 15 mm. pressure (Found: C, 85.85; H, 12.95; H:C = 18.1:10. Calc. for $C_{10}H_{16}$: C, 86.85; H, 6.65%).

About half the remaining liquid (10 g.), which yielded no significant thiol fraction when thoroughly extracted with sodium hydroxide solution, was volatile at 15 mm. (b. p. 90–92°; n_D^{20} 1.4966). This product, a monosulphide of dihydromyrcene, could not be completely freed from the last traces of hydrocarbon by repeated fractionation under a good column; the sulphur content was accordingly unavoidably low (Found: C, 70.85; H, 10.7; S, 18.4; active H, 0.02. $C_{10}H_{16}S$ requires C, 70.5; H, 10.65; S, 18.85; active H, 0.0%). This monosulphide was necessarily of cyclic constitution but improbably structurally homogeneous (see p. 1523); it gave (but only in part) with methyl iodide a methiodide, m. p. 130° (decomp.) (Found: S, 10.0; I, 40.5. $C_{11}H_{21}SI$ requires S, 10.25; I, 40.65%).

The undistilled sulphurated residue (ca. 18.5 g.) was a very viscous, dark red oil, easily soluble in hydrocarbons, carbon disulphide, and ethyl alcohol. A separation of this product into two roughly equal parts was effected by extracting it with methyl alcohol. These parts, although fairly reproducible as regards elementary composition, were probably both mixtures of sulphides, since their analyses corresponded with no definite compound. The insoluble fractions obtained in successive separations were dark brown, viscous oils (Found: S, 30.2; 28.1, 28.55%), and the corresponding soluble fractions reddish-brown oils (Found: S, 25.6, 25.1, 24.6%). These materials possessed the same general characteristics as the polysulphides from the simple olefins.

Action of Sulphur on Geraniolene.—The geraniolene (b. p. 109–111°/12 mm.) was prepared from commercial citral, which was first purified by conversion into the corresponding bisulphite compound (see Hibbert and Cannon, *J. Amer. Chem. Soc.*, 1942, **64**, 119), then oxidised to geranic acid (b. p. 118–120°/0.1 mm.; n_D^{20} 1.4880) by means of silver oxide (see Bernhauer and Forster, *J. pr. Chem.*, 1936, **147**, 199), and finally decarboxylated by heating it at ca. 260° in a stream of nitrogen. The crude hydrocarbon, mixed with a little geranic acid, distilled during the decomposition. Several batches of hydrocarbon were united and rectified. The final product was colourless liquid, b. p. 35–36°/15 mm., n_D^{20} 1.4410.

The hydrocarbon (72 g.) was heated with sulphur (7.0 g.) in a steel rotating autoclave for 5 hrs. at 140°. The crude product yielded no thiol fraction when thoroughly extracted with sodium hydroxide solution; it contained, however, much unconsumed hydrocarbon (about $\frac{2}{3}$ of original bulk), which was recovered by distillation.

About half the liquid residue (ca. 14 g.) was distillable at 12 mm. pressure, so giving a colourless, sweet-smelling liquid similar to that obtained from dihydromyrcene and sulphur. This product, n_D^{20} 1.4840, like the dihydromyrcene derivative, retained obstinately in spite of repeated refractionations traces of hydrocarbon. In consequence the sulphur content was invariably slightly low. It boiled at 65.5–66°/12 mm. (Found: C, 69.5; H, 10.5; S, 19.9; active H, 0.02. $C_8H_{14}S$ requires C, 69.2; H, 10.3; S, 20.5; active H, 0.0%).

Desulphuration of Polysulphides.—The method of desulphuration devised by Mazingo *et al.* (*loc. cit.*), employing Raney nickel powder prepared in the recommended way, was followed. The sample of nickel used evolved, on test, 116 c.c. of hydrogen per g. on being heated in butyl phthalate suspension at 220°. The sulphur compound (ca. 6 g.), dissolved in a little freshly-distilled cyclohexane, was dropped into a layer of freshly-distilled cyclohexane which acted as covering for the pyrophoric nickel (ca. 120 g.). Minute bubbles of gas were liberated immediately the sulphide was added. Gentle refluxing of the mixture for 3 hours completed the reaction, whereupon the solvent was removed by careful decantation, the nickel was extracted several times by boiling cyclohexane, and the solvent distilled from the united cyclohexane liquors through a column. The sulphides so treated were dicyclohexenyl sulphide (see below), and specimens of the total sulphuration products (freed from unconsumed hydrocarbon) derived from cyclohexene, 1-methylcyclohexane and isobutylene. In no case did any high-boiling hydrocarbon (representing a di- or poly-molecular derivative of the olefin originally sulphurated) or any sulphide remain.

Synthesis of Sulphides, Polysulphides, etc.—(1) 3:3'-Dicyclohexenyl sulphide. *N*-Bromosuccinimide (73.2 g.), prepared by the method of Ziegler *et al.* (*Annalen*, 1942, **551**, 80), and cyclohexene (206 c.c.) were gently refluxed for 20 mins. in pure carbon tetrachloride (300 c.c.) in the presence of a trace of benzoyl peroxide. Succinimide, which was insoluble in the tetrachloride, was gradually precipitated and was finally filtered off. The solvent was distilled off through a column and the residue fractionated. About 40 g. of almost colourless 3-bromocyclohexene, b. p. 60–61°/15 mm., n_D^{20} 1.5395, were collected (Found: C, 44.85; H, 5.7; Br, 49.3. Calc. for C_6H_9Br : C, 44.75; H, 5.65; Br, 49.6%).

3-Bromocyclohexene (12 g.), powdered sodium sulphide (5 g.), and alcohol (15 c.c.) were sealed in a Carius tube and heated to 100° for 4 hrs. The liquid in the cooled tube was filtered, diluted with ether, washed with water, dried (K_2CO_3), and the ether distilled. The residue, when distilled at ca. 0.1 mm. pressure gave about 4.5 g. of a colourless liquid, b. p. 81–82°, n_D^{20} 1.5506, of not unpleasant smell. This was 3:3'-dicyclohexenyl sulphide (Found: C, 74.15; H, 9.45; S, 16.35. $C_{12}H_{18}S$ requires C, 74.2; H, 9.35; S, 16.35%).

(2) cycloHexyl cyclohexenyl sulphide. This was formed by the action of lead cyclohexyl mercaptide on 3-bromocyclohexene. cycloHexanethiol (20 g.), prepared by the hydrolysis of cyclohexyl thiolacetate with alcoholic potassium hydroxide (Cunneen, *J.*, 1947, 134), was converted into its lead salt by shaking it for some hours in a stoppered vessel with excess of aqueous lead acetate. The precipitated yellow mercaptide was filtered off, well washed, dried at reduced pressure, and then suspended in alcohol (4000 c.c.). To the suspension was added 3-bromocyclohexene (29 g.), and the whole refluxed for 1 hr. on a water-bath. After filtration, most of the alcohol was distilled off through a column, and the concentrated alcoholic residue poured into water and extracted with ether. The extract was washed with water, dried ($CaCl_2$), and distilled. Much unchanged thiol passed over first, and then a colourless liquid, b. p. 69–70°/0.1 mm., n_D^{20} 1.5317, of not unpleasant smell. The latter was cyclohexyl cyclohexenyl sulphide (Found: C, 73.35; H, 10.2; S, 16.15. $C_{12}H_{20}S$ requires C, 73.4; H, 10.25; S, 16.3%).

(3) Propyl allyl sulphide. *n*-Propanethiol (45 g.) was converted into its lead salt as above, and the dried salt suspended in alcohol. To the suspension allyl bromide (70 g.) was added with shaking, and the whole refluxed for 1 hr. The resulting liquor was filtered from insoluble lead salts, poured into water, and extracted with ether. The extract was washed with water, dried ($CaCl_2$), and distilled at atmospheric pressure. The distillate (30 g.), a colourless mobile liquid, b. p. 138–140°/755 mm., was propyl allyl sulphide (Found: C, 61.9; H, 10.4; S, 27.7. $C_6H_{12}S$ requires C, 62.0; H, 10.4; S, 27.55%).

(4) cycloHexene thioepoxide (episulphide). This was obtained by the interaction of 1-chloro-2-thiocyanocyclohexane and sodium sulphide ($C_6H_{10}ClSCN + Na_2S \rightarrow C_6H_{10}S + NaCl + NaSCN$). Lead thiocyanate (235 g.) was dried, placed in a 1-l. flask, and covered with dry carbon tetrachloride (600 c.c.) to which cyclohexene (49 g.) had been added. The mixture was thoroughly stirred while phenyl iododichloride (153 g.) was added in small amounts during about 45 mins., and thereafter for 1 hr. The product was then filtered from insoluble lead salts, shaken with sodium thiosulphate solution to remove free dithiocyanogen, and washed as well as possible with water (the formation of emulsions gave trouble). The carbon tetrachloride solution was dried ($CaCl_2$), filtered from polythiocyanogen, and distilled. The solvent and any iodobenzene formed in the reaction were removed at reduced pressure; the residue, consisting of 1-chloro-2-thiocyanocyclohexane, distilled at 90–92°/0.1 mm. as a colourless liquid, after a forerun of 3 g. had been rejected (Found: C, 47.85; H, 5.8; N, 8.15; S, 18.3; Cl, 19.95. $C_6H_{10}NCIS$ requires C, 47.85; H, 5.75; N, 8.0; S, 18.2; Cl, 20.2%). n_D^{20} 1.5284, $[R]_D^{20}$ 44.86.

The chlorothiocyano-cyclohexane (31 g.) was dissolved in absolute alcohol (120 c.c.), and powdered sodium sulphide (25 g.) added. The mixture, contained in a 250-c.c. flask, was thoroughly stirred and refluxed on a water-bath for 2 hours. The cooled product was poured into water and extracted several


times with ether. The extract was dried (K_2CO_3), filtered, and the solvent distilled. The residue on distillation at 15 mm. pressure gave *cyclohexene thioepoxide* as a colourless mobile oil of distinctive odour, b. p. 56–57°, n_D^{20} 1.5350 (Found: C, 63.05; H, 8.85; S, 27.95. $C_6H_{10}S$ requires C, 63.1; H, 8.8; S, 28.05%).

(5) *Diethyl tetrasulphide*. Sodium tetrasulphide (23 g.), prepared by the method of Rule and Thomas (J., 1914, 105, 777), freshly-distilled ethyl iodide (60 g.), and absolute alcohol (90 c.c.) were refluxed on a water-bath for 2 hours in a slow stream of nitrogen. The product, when cool, was poured into water, and the precipitated oil extracted with benzene. The extract was dried (K_2CO_3), and the benzene distilled off. The oily residue, on distillation at 0.1 mm., passed over mainly at 43–45°, giving an evil-smelling, yellow oil, b. p. 43–45°, n_D^{20} 1.6105. This was undoubtedly slightly impure diethyl tetrasulphide (Found: S, 67.4. Calc. for $C_4H_{10}S_4$: S, 68.8%), which Riding and Thomas (J., 1923, 123, 3271; 1924, 125, 2463), probably owing to the technique adopted, failed to isolate after carrying out the same reaction. A small forerun and a residue, obtained as by-products, may well have represented the corresponding di- and penta-sulphide which were reported by Riding and Thomas to be formed. Comparison of the product with that obtained by the action of sulphur monochloride on ethanethiol (cf. Chakravarti, J., 1923, 123, 966), including spectroscopic examination in U.V. light by Dr. H. P. Koch, disclosed no essential difference between the two, although the latter appears to be freer from impurities (see Part IV).

(6) The following thio-compounds required for comparison with products derived by interaction of olefins and sulphur, and for infra-red spectroscopic observations, were synthesised by methods fully described in the literature: Thiols, ethyl, *n*-butyl, and *cyclohexyl*; sulphides, di-*n*-propyl, di-*n*-butyl, diallyl, dicrotyl; disulphides, di-*n*-butyl, dibenzyl.

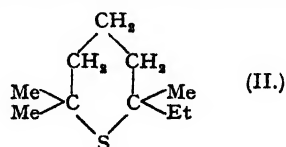
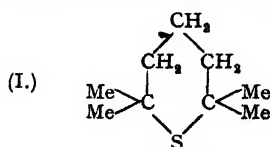
Infra-red Spectra.—The following report on the characteristics of thio-compounds has been furnished by Dr. G. B. M. Sutherland and Mr. N. Sheppard.

(1) *The Products of the sulphur-cyclohexene reaction*. The infra-red spectra of *cyclohexanethiol*, *dicyclohexyl sulphide*, 3 : 3'-*dicyclohexenyl sulphide*, and *cyclohexene episulphide* were compared with a series of ten fractions of the reaction products.

In no case was *cyclohexene episulphide* detectable in the reaction products, and only one of the "monosulphide" fractions showed the presence of *cyclohex-2-enyl* groups, . In most cases

the strong bands in the spectra were nearly all those of *cyclohexyl* groups, showing that such saturated groups predominated, but in addition every sample showed "unsaturation" bands due to C=C valency vibrations between 1590 and 1600 cm^{-1} , which are in the position generally associated with unsaturation of a conjugated type. No other olefinic groups were detected.

(2) *The reaction products of sulphur with geraniolene and dihydromyrcene*. The infra-red spectra of these products were compared with those of the saturated products obtained from the reaction of the same hydrocarbons with hydrogen sulphide (Sheppard and Sutherland, this vol., p. 1540). Two general points were noticeable: (a) Bands at 890 cm^{-1} indicated the presence of double bonds of the type $CRR'CH_2$ in the sulphur products. (b) There was a strong general resemblance in both cases between the spectra of the products of the reaction with sulphur and those with hydrogen sulphide. In the case of the geraniolene-sulphur product a noticeable splitting of the 1370 cm^{-1} band indicated a preponderance of *gem*-dimethyl groups (Sheppard and Sutherland, *loc. cit.*), and was further evidence for the similarity of the two products (see below). As the purification of the hydrogen sulphide products led to their identification as 2 : 2 : 6 : 6-tetramethyltetrahydrothiopyran (I) and 2 : 2 : 6-trimethyl-6-ethyltetrahydrothiopyran (II), it seems reasonable to assume that the carbon skeletons of the sulphur products



are closely related. On chemical grounds one would expect that the sulphur products would contain a double bond in the molecule, but our spectroscopic data are insufficient to decide this point. However, in view of the fact that the spectra of *cyclohexyl* and *cyclohexenyl* groups have many features in common, the spectroscopic data would be consistent with the presence of the above saturated compounds in the products or, alternatively, with the presence of similar compounds containing a double bond in the ring. Since $CRR'CH_2$ groups are not obtainable with carbon skeletons of the above type, these bands presumably arise from another molecular species in the product.

Reductive Scission of Sulphides.—(a) *Action on saturated dialkyl sulphides*. Redistilled di-*n*-butyl sulphide (1 g.; 1 mol.) was dissolved in absolute alcohol (50 c.c.), and sodium (5 g.; 3.2 atoms) added in portions. The alcohol was kept boiling until the sodium had all dissolved, whereupon the product was cooled, poured into water, and the aqueous liquor extracted once with ether to remove traces of unchanged sulphide. The alkaline liquor was then acidified with hydrochloric acid and several times extracted with ether to remove all thiol formed in the reduction. The ethereal extract was freed from traces of mineral acid by washing it with water, and afterwards the content of thiol determined by means of silver nitrate following the procedure of Bell and Agruss (*loc. cit.*). It was found that no appreciable reduction of sulphide to thiol had occurred. The experiment was repeated with pure di-*n*-propyl sulphide, with the same result.

(b) *Action on dialkenyl sulphides*. This was examined with diallyl and *dicyclohexenyl* sulphides. The amount of hydrogen sulphide and thiol (respectively) produced by reaction were determined from the total yield of -SH groups (including hydrogen sulphide) and the yield of thiol. These values were determined by extracting the hydrogen sulphide and thiol together from one aliquot part of the acidified (H_2SO_4), sulphide-free reduction liquor by means of benzene, and precipitating the hydrogen sulphide

from another by means of cadmium chloride, before extracting the thiol from the filtered liquor by means of ether. The details were essentially those of Bell and Agruss (*loc. cit.*). Diallyl sulphide (0.20 g.) became completely reduced, giving approximately equimolecular amounts of hydrogen sulphide (0.0260 g.) and thiol (0.062 g., calc. as allylthiol). Dicyclohexenyl sulphide (0.33 g.) was similarly completely reduced, giving hydrogen sulphide (0.024 g.) and thiol (0.13 g., calc. as cyclohexenthiol).

(c) *Action on alkyl alkenyl sulphides.* These sulphides gave no hydrogen sulphide on reduction, which was incomplete. cyclohexyl cyclohexenyl sulphide (0.26 g.) gave thiol (doubtless cyclohexyl, 0.091 g.; corresponding to ca. 60% reduction); propyl allyl sulphide (0.105 g.) gave thiol (doubtless propyl, 0.033 g., corresponding to ca. 50% reduction).

(d) *Action on cyclic sulphides.* The cyclic sulphides from dihydromyrcene and geraniolene were separately reduced in the usual way. Reduction proved to be very incomplete in each case; no hydrogen sulphide was produced but a moderate yield of alkali-soluble thiol was formed from each sulphide.

(e) *Action on thioepoxides.* This was examined only in the instance of cyclohexene thioepoxide. The latter (0.148 g.) gave both hydrogen sulphide (0.010 g.) and thiol (doubtless cyclohexyl, 0.08 g.).

Action of methyl iodide on monosulphides. The sulphide was in each case mixed with an equal volume of the reagent and kept in the dark overnight. A typical saturated sulphide, dicyclohexyl sulphide, gave in good yield the corresponding sulphonium iodide, $\text{SMe}(\text{C}_6\text{H}_{11})_2\text{I}$, m. p. 111°. Three dialkenyl sulphides, viz., diallyl, dicrotyl, and 3 : 3'-dicyclohexenyl sulphide, all readily gave crystals of trimethylsulphonium iodide, m. p. 204–207° (decomp.), identical with the compound prepared by union of methyl iodide and methyl sulphide, but no stable sulphonium compound. Two alkyl alkenyl sulphides, viz., cyclohexyl cyclohexenyl sulphide and propyl allyl sulphide, both gave non-crystallising oily products.

The monosulphide from the cyclohexene-sulphur reaction gave much oily material, like the alkyl sulphides, but also a little dicyclohexylmethylsulphonium iodide, m. p. 110° (mixed with authentic specimen, 110°). The cyclic sulphide from dihydromyrcene gave with methyl iodide an oil which slowly crystallised: the resulting solid (colourless prisms, m. p. 130°, from ether-alcohol) was a *methiodide* of dihydromyrcene monosulphide (Found: C, 42.0; H, 7.0; I, 40.5. $\text{C}_{11}\text{H}_{21}\text{SI}$ requires C, 42.3; H, 6.8; I, 40.65%). The cyclic sulphide from geraniolene likewise gave with methyl iodide an oil that slowly crystallised: the solid (colourless prisms, m. p. 120°, from ether-alcohol) was a *methiodide* of geraniolene monosulphide (Found: C, 39.9; H, 6.85; I, 42.25; S, 10.45. $\text{C}_{10}\text{H}_{19}\text{SI}$ requires C, 40.25; H, 6.45; I, 42.55; S, 10.75%).

cyclohexene episulphide gave with methyl iodide in a few hours much trimethylsulphonium iodide, m. p. 204–207° (Found: C, 17.55; H, 4.45. Calc. for $\text{C}_3\text{H}_5\text{SI}$: C, 17.7; H, 4.45%).

Removal of Polysulphide Sulphur by Chemical Reagents.—(a) *With sodium hydroxide.* The sample of sulphide was placed in a small flask (ca. 10 c.c.) together with 10% or 40% alkali (6 c.c.) and a few c.c. of 0.1% sodium stearate to act as wetting agent. The air space was filled with nitrogen, and the closed vessel mechanically shaken in an oil-bath adjusted to the desired temperature. After the period of treatment was completed the reaction liquor was poured into water, the oily sulphide extracted with benzene, the benzene solution washed well with water and dried (K_2CO_3), and the dry solution filtered and freed from solvent in a vacuum without heating. The decrease in sulphur content due to the action of the alkali was determined by analysis of the specimen before and after treatment in preference to determining the amount of sulphide formed in the reaction.

Typical examples of the effect of the alkali in removing sulphur are the following: The tetrasulphide from cyclohexene decreased in sulphur content from 43.15 to 41.0% in 3 hrs. at 60° with 10% alkali, and from 43.15 to 40.15% in 3 hours at 80° with 40% alkali. The tetrasulphide from cyclohexene decreased in sulphur content from 36.4 to 33.65% in 3 hrs. at 80° with 40% alkali. Diethyl tetrasulphide (from sodium tetrasulphide and ethyl iodide) decreased in sulphur content from 67.4 to 51.5% in 3 hrs. at 80° with sodium hydroxide, so giving nearly pure diethyl disulphide (S, 52.5%).

(b) *With sodium sulphite.* The weighed sample of sulphide (usually ca. 0.1 g.) was placed in 10% "AnalaR" sodium sulphite solution (100 c.c.) together with 0.1% sodium stearate (ca. 5 c.c.) to act as wetting agent. The solution was boiled for 2.5 hrs. during which nitrogen was slowly bubbled through. Organic matter was extracted with chloroform; then the aqueous phase was cooled at 0°, and 40% formaldehyde solution added to combine with the excess of sodium sulphite. Glacial acetic acid (10 c.c.) and 1% starch solution (3 c.c.) were next added, and the solution titrated with N/10-iodine solution to determine the yield of sodium thiosulphate and hence the amount of sulphur removed (1 mol. of $\text{Na}_2\text{S}_2\text{O}_3 \equiv 1$ atom of S). The following are typical results, losses being given in terms of total sulphur: Ethyl tetrasulphide (from sodium tetrasulphide and ethyl iodide) lost 47.5% (i.e., 1.9 atoms). The polysulphide mixture (excluding cyclic monosulphide) obtained in the geraniolene-sulphur reaction lost 10.8%. The corresponding polysulphide mixture from dihydromyrcene lost 6.4%. Dibutyl tetrasulphide lost 30.1%, and cyclohexene episulphide 45%.

Thermal Decomposition of Polysulphides.—Attempted distillation at ca. 0.1 mm. of the sulphurated products from cyclohexene and 1-methylcyclohexene gave but little distillate (a little monosulphide and no thiol or hydrogen sulphide) unless the temperature of the heating bath was allowed to rise well above 140°. Prolonged heating at higher temperatures caused a slow but progressive distillation of monosulphide, thiol, and hydrogen sulphide. The tendency to decomposition of the monosulphide-free sulphurated product from cyclohexene was examined at 160–170° by heating it in sealed tubes for 5 hours. The tubes were cooled in liquid air before being opened, and the main bulk of hydrogen sulphide present was allowed to evaporate slowly into lead acetate solution. The lead sulphide was filtered off, dried, and weighed. The thiol and residual hydrogen sulphide were estimated by utilising the method of Bell and Agruss (*loc. cit.*). In a typical experiment 13 g. of the sulphuration product yielded hydrogen sulphide (3.8 g.), thiol (2.5 g.), volatile sulphides (mainly monosulphide, 3.3 g.), and a small amount of non-volatile solid which was easily soluble in benzene (3.2 g.). In another experiment 5.9 g. of thio-product, after being kept at 130° and 10⁻³ mm. for 30 hrs. to ensure that no free thiol or lower sulphides were present, gave, on being heated in a sealed tube at 180–190° for 5 hrs., hydrogen sulphide (1.7 g.), thiol (1.2 g.), sulphides (mainly mono-, 1.4 g.), and a dark residue of solid (mainly crystalline) thiohydrocarbon (1.4 g.). The residue, like all residues similarly obtained by the thermal decomposition of

sulphurated cyclohexene, had a much reduced H:C ratio (Found: C, 56.35; H, 3.75; S, 39.7%; H:C = 4.75/6).

This paper forms part of a programme of research undertaken by the Board of the British Rubber Producers' Research Association.

THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
WELWYN GARDEN CITY, HERTS.

[Received, January 15th, 1947.]

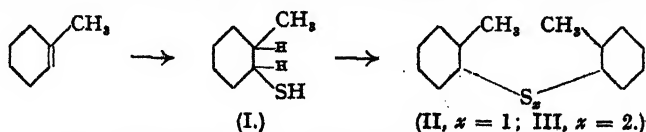
299. *The Reaction of Sulphur and Sulphur Compounds with Olefinic Substances. Part II. Mechanism of the Reaction of Hydrogen Sulphide with Mono-olefins, Di-isoprenes, and Rubber.*

By RALPH F. NAYLOR.

Hydrogen sulphide unites with mono- and di-olefins under pressure to give *normal* adducts when reaction is conducted in the presence of sulphur or a metallic sulphide as catalyst, and *abnormal* adducts when it is promoted under the influence of ultra-violet light. The adducts of both types include alkanethiols and alkyl sulphides and disulphides. The principal reaction products from the two di-isoprenes, dihydromyrcene and geraniolene, are cyclic sulphides of the tetrahydrothiopyran series, each being derived from a single molecule of the diolefin; corresponding products derived from two molecules of the diolefin are formed in much smaller yield. Rubber also gives sulphides of the latter (cross-linked) kind, formed by the linking of two or more polyolefin molecules by sulphur.

APART from the intrinsic interest of the reactivity of hydrogen sulphide with olefins, a knowledge of this reactivity is, as indicated in Part I (preceding paper), of considerable importance in the study of the reaction of sulphur with unsaturated compounds. In marked contrast to the wealth of literature on the addition of hydrogen bromide to olefins, there is very little work recorded on the corresponding reactions of hydrogen sulphide. Such accounts as are published indicate that the addition of hydrogen sulphide is difficult to effect, and that catalysts are invariably required. Among the various catalysts found to be effective are silica gel (Mailhe and Renaudie, *Compt. rend.*, 1932, **195**, 391), nickel on kieselguhr, and certain nickel salts (Duffey, Snow, and Keyes, *Ind. Eng. Chem.*, 1934, **26**, 91; Barr and Keyes, *ibid.*, p. 1111), iron oxide and sulphide (Boëseken and Van der Linde, *Rec. Trav. chim.*, 1935, **54**, 739), and sulphur (Jones and Reid, *J. Amer. Chem. Soc.*, 1938, **60**, 2452). The yields of addition products have seldom been high, and the direction of addition has been found in each case to follow the Markownikow rule, although a proportion of *abnormal* addition products was obtained in high-temperature heterogeneous reactions (Barr and Keyes, *loc. cit.*); this probably arose by partial isomerisation of the initial adduct. Recently, however, Vaughan and Rust (*J. Org. Chem.*, 1942, **7**, 472), by ultra-violet irradiation of mixtures of olefins and liquid hydrogen sulphide, have obtained *abnormal* adducts in a short reaction time, without the aid of the high temperatures and pressures found necessary for *normal* addition.

Since it was observed by Jones and Reid (*loc. cit.*) that the normal addition of hydrogen sulphide proceeds far less readily with cyclohexene than with simple aliphatic olefins, it was not surprising to find that photo-addition of liquid hydrogen sulphide to 1-methylcyclohexene gave poor yields. As Pyrex glass, which was used for the reaction tubes, does not transmit light below 2900 Å., whereas hydrogen sulphide is split into radicals only by wave-lengths of 2800 Å. or less, it was necessary to add acetone as a photo-sensitiser. The products were a thiol and sulphide, and by analogy with the work of Vaughan and Rust, it may be assumed that these were 1-methylcyclohexane-2-thiol (I), and di-2-methylcyclohexyl sulphide (II). In one experiment the sulphide fraction was found to contain some disulphide (III), which although present in insufficient quantity for separation, was indicated to be present by analytical evidence. Although no previous reference has been made to the formation of disulphides in such reactions,

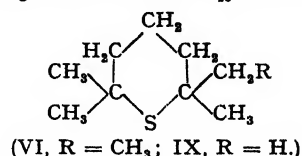
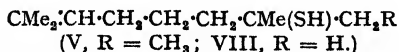
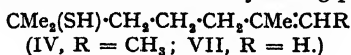


it seems evident that it has arisen either by combination of two mercapto-radicals or by oxidation of the initially formed thiol.

The only recorded work on the catalysis of hydrogen sulphide addition by sulphur (Jones and Reid, *loc. cit.*) suggests that the latter is one of the best catalysts for normal addition, but the relatively large quantities of catalyst then used introduce doubt as to how far the sulphur is itself reacting with the olefins and how far catalysing the addition of hydrogen sulphide. In addition, this work was conducted at 180°, at which temperature there is appreciable decomposition of some di- and poly-sulphides (see Part I; also Hinsberg, *Ber.*, 1910, 43, 1874). It has now been confirmed that small quantities of sulphur catalyse the addition of hydrogen sulphide to isobutylene at ca. 140°; some reaction took place in absence of sulphur, but this was probably due to the catalytic effect of ferrous sulphide formed on the walls of the steel autoclave used. The reaction products were identified as being *tert.*-butyl derivatives formed by "normal" addition of the reagent to the double bond, and included di-*tert.*-butyl disulphide as well as the corresponding monosulphide and thiol. The yield of disulphide was greater than could have arisen by reaction of the sulphur catalyst with isobutylene, and it was still formed when the catalyst was omitted. The possibility of oxidation of the initially formed thiol was investigated by heating *tert.*-butanethiol with air in a sealed tube; no disulphide could be detected although there was some decomposition of the thiol into *tert.*-dibutyl sulphide and hydrogen sulphide. Rigorous exclusion of air from the isobutylene-hydrogen sulphide reaction mixture did not prevent formation of the disulphide, so the only possible mode of reaction seems to be oxidation of the thiol with concurrent reduction (hydrogenation) of the olefin, as reported by Williams and Allen (U.S.P. 2,052,268; *Chem. Abs.*, 1936, 30, 7122) for similar hydrogen sulphide additions.

*cyclo*Hexene reacted with hydrogen sulphide in presence of a sulphur catalyst in a manner analogous to isobutylene, although the *cyclo*hexanethiol first produced appeared to add more readily than hydrogen sulphide to the olefin, since dicyclohexyl sulphide constituted the main product. An attempt to catalyse the addition of hydrogen sulphide to 1-methylcyclohexene by ethyl dihydrogen phosphate, after the suggestion of Bähr and Corr (D.R.-P. 708,261), was unsuccessful.

Sulphur-catalysed addition of hydrogen sulphide to polyisoprenes occurred more readily than it did to hydroaromatic hydrocarbons. Dihydromyrcene, $\text{CH}_3\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\cdot\text{CHMe}$, reacted to give a quantity of alkali-soluble material which was too small to permit of isolation of this thiol, but gave a 20% yield of an alkali-insoluble compound of formula $\text{C}_{16}\text{H}_{20}\text{S}$. Of the possible structural formulæ, (IV), (V), and (VI), assignable to this product, (VI), which is formed from (IV) or (V) by an intramolecular addition reaction, seemed the most likely in view of the insolubility of the product in alkali. Inter-molecular addition reaction yielding products containing more than one C_{10} -unit occurred



to the extent of only 1–2%, but there appeared to be some unimolecular disulphide ($\text{C}_{10}\text{H}_{20}\text{S}_2$), which was present in insufficient quantity for isolation. Similar results were obtained by interaction of geraniolene, $\text{CH}_3\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\cdot\text{CH}_2$, with hydrogen sulphide, the main product in this case being a thio-compound $\text{C}_9\text{H}_{18}\text{S}$, represented by (VII), (VIII), or (IX). Attempts to obtain characteristic metallic salts or metallic-salt addition compounds were unsuccessful. The infra-red absorption spectrum of this thio-compound was radically different from that of the parent geraniolene, suggesting that a complete change of structure, such as is involved in the formation of a tetrahydrothiopyran ring, might have occurred. An attempt to establish this ring structure by correlation of the spectrum with that of pentamethylene sulphide was unsuccessful, as the latter exhibited an altogether different spectrum from that of the hydrogen sulphide reaction products. Synthetic 2 : 2 : 6 : 6-tetramethyltetrahydrothiopyran (see this vol., p. 1106), although analytically identical with the hydrogen sulphide reaction product, showed differences in boiling point and refractive index, and had a characteristic infra-red absorption spectrum,* which could not be correlated with that of the reaction products. In particular, the latter exhibited absorption associated with unsaturated groupings of the types $\text{CMeR}\cdot\text{CH}_2$ and $\text{CRR}\cdot\text{CHR}$ and with thiol groups.

* Examination of the infra-red absorption spectra of the compounds described in this paper was carried out at Cambridge by Dr. G. B. M. Sutherland and Mr. N. Sheppard. The details of the spectra are discussed by these authors in the following paper.

Similar results were obtained with the dihydromyrcene-hydrogen sulphide product. The possibility of the unsaturation being due to the presence of small amounts of unchanged olefin was excluded by two experiments. Dihydromyrcene is a mixture of 2:6-dimethylocta-2:6-diene, 2:6-dimethylocta-2:6(10)-diene, and possibly 2:6-dimethylocta-1:6-diene and therefore shows absorption characteristic of $\text{CMeR}'\text{CH}_2$ grouping. The pure 2:6-isomer (which exhibits no such absorption) was prepared by sodium-ammonia reduction of geraniol (Chablay, *Ann. Chim.*, 1917, 8, 145; Dupont, Dulou, and Desreux, *Bull. Soc. chim.*, 1939, 6, 84) and reacted with hydrogen sulphide in the presence of sulphur. The resulting product also showed bands characteristic of $\text{CMeR}'\text{CH}_2$ groups, although it was established that no isomerisation of the recovered hydrocarbon had occurred. Also, examination of suitable mixtures showed that introduction of small amounts of dihydromyrcene to the synthetic thiopyran (IX) did not affect the absorption spectrum.

Substitution of aluminium sulphide for sulphur as a catalyst in the reaction of 2:6-dimethylocta-2:6-diene with hydrogen sulphide gave rise to products similar to the foregoing, but there was isolated in addition, 2:6-dimercapto-2:6-dimethyloctane, $\text{CMe}_2(\text{SH})\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{SH}$ (X). The main product, $\text{C}_{10}\text{H}_{20}\text{S}$, showed considerable difference in the absorption attributable to unsaturation from that described above, the predominant group now being $\text{CRR}'\text{CHR}''$ with very little $\text{CMeR}'\text{CH}_2$. It is evident, therefore, that the $\text{CMeR}'\text{CH}_2$ group arises by reaction of the sulphur itself and not of the hydrogen sulphide. That cyclic sulphides containing this group are in fact among the products of reaction of sulphur with dihydromyrcene has been indicated in Part I (*loc. cit.*).

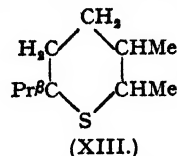
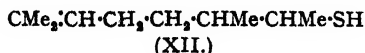
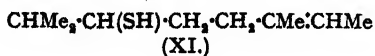
The improbability of the occurrence in significant degree of a radical mechanism leading to "abnormal" addition in the sulphur-catalysed or metal sulphide-catalysed hydrogen sulphide reaction was indicated by demonstrating that the type of reaction obtained with 2:6-dimethylocta-2:6-diene was unaffected by the presence of quinol (polyisoprenes usually contain small quantities of peroxide which might catalyse the abnormal addition). However, the ratio of thiol to cyclic sulphides was increased.

In spite of the alkali-insolubility of the compounds $\text{C}_{10}\text{H}_{20}\text{S}$ and $\text{C}_9\text{H}_{18}\text{S}$, Zerewitinoff determinations by the micro-method of Bolland (*Trans. Inst. Rubber Ind.*, 1941, 16, 267) indicated the presence of varying amounts of active hydrogen, presumably in the form of thiol groups* as had already been indicated by the infra-red spectra. The susceptibility of this method to traces of compounds of low molecular weight containing active hydrogen rendered it less reliable than the method recently described by Turk and Reid (*Ind. Eng. Chem. Anal.*, 1945, 17, 713) involving titration of a solution of the thiol against a solution of cupric butyl phthalate. The presence of the thiols (IV) and (V), and (VII) and (VIII), in amounts up to 40% of the total $\text{C}_{10}\text{H}_{20}\text{S}$ and $\text{C}_9\text{H}_{18}\text{S}$ fractions was thus demonstrated. A modification of the analytical method allowed cupric butyl phthalate to be used for the qualitative removal of the thiol from the mixtures obtained by the aluminium sulphide-catalysed reactions, and this resulted in the isolation in a nearly pure state of 2:2:6-trimethyl-6-ethyltetrahydrothiopyran (VI) and 2:2:6:6-tetramethyltetrahydrothiopyran (IX) (see this vol., p. 1106). These two compounds exhibited absorption spectra similar to each other in the infra-red, and in both, all bands associated with unsaturation and thiol groups had disappeared. The geraniolene-hydrogen sulphide product (IX) corresponded in boiling point with the synthetic 2:2:6:6-tetramethyltetrahydrothiopyran and exhibited similar absorption [notably that associated with the >CMe_2 group which is masked in (VI) by single methyl groups] with the addition of some other absorption bands. These extra bands are almost certainly due to reaction products of small amounts of isomers of geraniolene, for, since the preparation of this involves decarboxylation of geranic acid at 270° , a partial isomerisation of the olefin is very probable. This view is confirmed by the nitrous acid test for thiols (Rheinboldt, *Ber.*, 1926, 59, 1311; 1927, 60, 184), which indicates that while all the dihydromyrcene products contain only tertiary thiols, those from geraniolene contain at least some primary or secondary thiols. Complete agreement was obtained between the infra-red spectrum of the cyclic sulphide from the reaction of 2:6-dimethylocta-2:6-diene and hydrogen sulphide and that of synthetic 2:2:6-trimethyl-6-ethyltetrahydrothiopyran (see this vol., p. 1106).

The abnormal addition of hydrogen sulphide to 2:6-dimethylocta-2:6-diene has been effected by U.V. irradiation of the reactants in the liquid phase, acetone being used as a photo-sensitiser. As in other additions, the main product was a liquid of formula $\text{C}_{10}\text{H}_{20}\text{S}$, which was shown to consist of an approximately 1:1 mixture of the monothiols (XI, XII) and

* It is known from earlier work that the acidity of thiols decreases progressively with increasing molecular weight (Birch and Norris, *J.*, 1925, 127, 901).

2 : 3-dimethyl-6-isopropyltetrahydrothiopyran (XIII). Removal of the thiol by cupric butyl phthalate led to the isolation of a small quantity of the thiopyran (XIII), the absorption



spectrum of which exhibited a number of differences from those of the earlier products. In particular, there was some characteristic absorption which was absent in the *normal* adduct (VI), and *vice versa*. Similar differences in the absorption spectrum were exhibited by 3 : 7-dimercapto-2 : 6-dimethyloctane, $\text{CHMe}_2\cdot\text{CH}(\text{SH})\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CHMe}\cdot\text{SH}$ (XIV), which was also isolated in small yield from the reaction product.

In addition, an intermolecularly derived *sulphide*, $\text{C}_{20}\text{H}_{40}\text{S}_2$, formed by union of two monomercapto-units, was isolated; its analytical figures and %SH content showed it to be a compound of the type (XV), the points of addition of the SH group, on the one hand, and of the



union through the S atom, on the other, allowing of three possible isomers (see p. 1539). This is confirmed by its infra-red absorption spectrum, which includes the characteristic absorptions of ·SH and CRR'·CHR'' groups.

Yields of the various derivatives with the olefins mentioned are indicated in Table I.

TABLE I.
Addition of hydrogen sulphide to olefins.

Olefin.	Molecular proportions (olefin = 1) :		Reaction conditions :		Pressure, atm., of H_2S at working temp.	Yields of products, %.			Undistill- able inter- molecular sulphides.
	H_2S .	Catalyst.	hrs.	temp.		Alkali- sol. thiol.	Sulphide.	Disul- phide.	
<i>iso</i> Butylene	1	0.015 (S)	14	150°	45	7 ¹	4	3	0.5
"	1	—	18	130—150	45	2 ¹	—	0.5	Negligible
"	1	—	14	140	45	2 ¹	0.5	0.5	"
<i>cyclo</i> Hexene	2.5	0.015 (S)	24	150	110	2.5	12	1.5	"
Dihydromyrcene	2	0.03 (S)	20	130	45	Negligible	$\text{C}_{10}\text{H}_{20}\text{S}$ or $\text{C}_9\text{H}_{18}\text{S}$ fraction.	2	1.5
"	2	0.03 (S)	22	160	45	"	13	3	2
Geraniolene	2	0.03 (S)	24	150	50	"	18	1	1.5
"	2	0.1 (Al_2S_3) (+ quinol)	26	150	45	"	14	0.1	1
2 : 6-Dimethylocta- 2 : 6-diene	2	0.03 (S)	22	140—150	45	Negligible	8	2	2
"	2	0.1 (Al_2S_3)	23	150—165	60	0.5	10	0.5	0.5
"	2	0.1 (Al_2S_3) (+ quinol)	24	150	50	2	8	2	2
"	1.2	0.15 (COMe_2) (U.V. irradiation)	4	15	15	2	22	—	5

¹ These figures are too low as some thiol was lost on evaporation of the *isobutylene*.

² Not separated.

It was hoped that addition of hydrogen sulphide to rubber might be effected by shaking a rubber solution with the gas while irradiating it with ultra-violet light. However, even after 4 hours' irradiation of a solution of sol rubber (obtained by diffusion of acetone-extracted crepe rubber into light petroleum) only 1.1% of sulphur had entered the molecule. Although quartz apparatus was being used, this figure was doubled when acetone was added as a sensitizer, and small amounts of gelled material separated, which contained up to 10% of sulphur. The best value represents the saturation of 48% of the double bonds of rubber if the sulphur is assumed to be present as monosulphide.

It has been shown by Jones and Reid (*loc. cit.*) that peroxides catalyse the abnormal addition of thiols to olefins. Evidence for the catalytic effect of benzoyl peroxide on the addition of hydrogen sulphide to rubber in the present work was inconclusive. However, it was shown that

the addition reaction initiated by ultra-violet light was substantially inhibited by the natural antioxidants in rubber. Quam's report (*J. Amer. Chem. Soc.*, 1925, 47, 103) that rubber dissolves in liquid hydrogen sulphide was confirmed with milled acetone-extracted crepe, and when the resultant solution was irradiated with ultra-violet light as before, it gave rise to a product containing 2.1% of sulphur. The addition of acetone much reduced the solubility of the rubber, but it increased the sulphur intake to 3.2%.

Solid rubber reacted with hydrogen sulphide both in the presence and in the absence of sulphur, but the latter reaction was probably catalysed by ferrous sulphide on the walls of the steel autoclave. This view was confirmed by the addition of hydrogen sulphide to rubber in the presence of ferrous sulphide and ferric oxide. Although the results obtained with dihydromyrcene and geraniolene suggest that the main reaction with polyisoprenes is intramolecular, there is always some intermolecular addition, and it may well be that this is facilitated in the case of rubber by the intermolecular entanglements of the long chains. A characteristic of all the products which have been obtained from rubber by hydrogen sulphide addition, even when the combined sulphur value is as low as 1%, is their complete insolubility in all organic solvents once they have been separated from solution. It therefore seems evident that intermolecular sulphide and disulphide links of the type observed with cyclohexene and isobutylene are being formed. That there is a tendency for the average molecular weight to rise is shown by the fact that the observed molecular weight of a sample of milled rubber rose from 137,000 to 153,000 on treatment with hydrogen sulphide involving the incorporation of only 1% of sulphur. Rubber samples containing 2—3% of sulphur, which had been formed by reaction of solid rubber with hydrogen sulphide, exhibited many of the characteristics of a sulphur-vulcanised rubber, and although the porosity of the product precluded tensile strength tests, selected portions of the sheet were capable of over 700% elongation with good recovery. An attempt to obtain a smooth sheet for such tests by working at atmospheric pressure was unsuccessful, owing to the slowness of addition. The results obtained on both the *abnormal* and *normal* addition of hydrogen sulphide to rubber are summarised in Table II.

TABLE II.
Addition of hydrogen sulphide to rubber.

Type of rubber.	Solvent.	Sol. concn., %.	Reaction conditions :		Catalyst or sensitiser.	S, %, in product.	
			Hrs.	Light.		Fractn. remaining in solution.	Insol. fractn.
Abnormal addition.							
Sol	Benzene	1	4	u.v.	—	1.1	—
Sol	"	1	4	"	5% COMe ₂	2.25	—
Sol	"	1	4	"	5% COMe ₂	2.65	10.1
Sol	"	1	4	"	Bz ₂ O ₂ & 5% COMe ₂	2.1	—
Crepe	"	1	4	"	5% COMe ₂	0.8	—
Milled acetone-extracted crepe	"	9	7.5	"	5% COMe ₂	1.0	{ 4.5 2.2
" " " " " " " "	"	1	4	daylight	—	0.15	—
" " " " " " " "	"	1	1	(at 75°)	Bz ₂ O ₂	0.30	—
" " " " " " " "	Liq. H ₂ S	1	0.4	u.v.	—	2.07	—
" " " " " " " "	"	1	0.4	"	5% COMe ₂	3.2	1.3
Normal addition.							
			Hrs.	Temp.	press., atm., of H ₂ S.		
Milled crepe	—	—	2	140°	30	—	{ 1.85 2.2
" " " " " " " "	—	—	2	140	30 ½% S	—	{ 2.7 2.8
" " " " " " " "	—	—	2	140—160	30	—	2.75*
" " " " " " " "	—	—	2	140—160	30 ½% S	—	3.25*
Milled acetone-extracted crepe	—	—	2	140—160	30	—	3.15*
Milled crepe	—	—	2	260	40	—	8.45
" " " " " " " "	—	—	48	140	1	—	0.5
" " " " " " " "	—	—	48	140	1 ½% S	—	0.8
Milled acetone-extracted crepe	cycloHexane	8	20	85—103	20 FeS & Fe ₂ O ₃	1.1	4.8

* After acetone extraction of the product.

EXPERIMENTAL.

(Microanalyses were carried out by Dr. W. T. Chambers, Miss H. Rhodes, and Miss E. Farquhar.)

Hydrogen sulphide was prepared and purified by Quam's method (*loc. cit.*).

1-Methylcyclohexene and Hydrogen Sulphide.—1-Methylcyclohexene (10 g.), liquid hydrogen sulphide (7 g.), and acetone (1 g.) were sealed in a Pyrex tube, and irradiated with ultra-violet light for 60 minutes at 0°. The product was extracted with 10% aqueous sodium hydroxide (50 ml.) and with ether. From the alkaline extract was obtained 1-methylcyclohexane-2-thiol (1 g.), which was distilled at 56°/14 mm.; it was an evil-smelling, colourless liquid, which froze when cooled to 0° (Found: C, 63.8; H, 10.8; S, 23.8. $C_7H_{14}S$ requires C, 64.6; H, 10.8; S, 24.6%). The neutral portion, which was very small, distilled at 106°/0.1 mm., and appeared to consist of a mixture of di-2-methylcyclohexyl sulphide and disulphide (Found: C, 69.8; H, 10.7; S, 18.5. Calc. for $C_{14}H_{26}S$: C, 74.3; H, 11.5; S, 14.2. Calc. for $C_{14}H_{24}S_2$: C, 65.1; H, 10.1; S, 24.8%).

isobutylene and Hydrogen Sulphide (Sulphur Catalyst).—A mixture of isobutylene (56 g.), solid hydrogen sulphide (38 g.), and sulphur (0.5 g.) was introduced into a steel autoclave and heated for 14 hours at ca. 150°. After evaporation of unchanged hydrocarbon the product (12.2 g.) contained *tert.*-butanethiol (6.0 g.), di-*tert.*-butyl sulphide (2.6 g.), di-*tert.*-butyl disulphide (2.8 g.), and a non-volatile residue (0.5 g.). The thiol was redistilled to give a liquid, b. p. 63°, n_D^{20} 1.4212, and identified as its mercuric salt, m. p. 159–160° (Found: S, 16.8. Calc. for $C_8H_{18}S_2Hg$: S, 16.9%). After thorough extraction with 10% aqueous alkali, the monosulphide distilled at 51°/16 mm. and had n_D^{20} 1.4511 (Found: C, 65.5; H, 12.3; S, 21.9. Calc. for $C_8H_{18}S$: C, 65.7; H, 12.3; S, 21.9%). Fractionation of the disulphide gave a liquid, b. p. 79–80°/16 mm., n_D^{20} 1.4928 (Found: C, 53.9; H, 10.2; S, 35.9. Calc. for $C_8H_{16}S_2$: C, 53.9; H, 10.1; S, 35.9%).

In absence of sulphur, 14 hours' heating of a mixture of isobutylene (56 g.) and hydrogen sulphide (38 g.) gave a product containing *tert.*-butanethiol (1 g.), di-*tert.*-butyl sulphide (0.6 g.), and di-*tert.*-butyl disulphide (0.7 g.). In a further similar experiment, when air was completely excluded, after 18 hours at 130–150° the product consisted of thiol (1.5 g.), disulphide (0.4 g.), and a negligible quantity of sulphide.

tert.-Butanethiol (2 g.) was heated in a sealed tube in presence of air for 14 hours at 140–150°; it was mainly unchanged but contained di-*tert.*-butyl sulphide (0.2 g.) and hydrogen sulphide.

cyclohexene and Hydrogen Sulphide (Sulphur Catalyst).—A mixture of cyclohexene (100 g.), hydrogen sulphide (100 g.), and sulphur (0.5 g.) was heated for 24 hours at ca. 150°. Fractional distillation of the product gave cyclohexanethiol (3.5 g.), dicyclohexyl sulphide (13.5 g.), dicyclohexyl disulphide (2.5 g.), and a residue (1.5 g.). The thiol was purified by conversion with 10% aqueous alkali into its sodium salt, whose solution was acidified with hydrochloric acid under nitrogen; the redistilled thiol had b. p. 41°/12 mm., n_D^{20} 1.4988 (Found: C, 62.1; H, 10.2; S, 27.3. Calc. for $C_6H_{12}S$: C, 62.0; H, 10.3; S, 27.6%). To an alcoholic solution of the thiol was added hot aqueous mercuric cyanide. The precipitated oil was dissolved in hot alcohol and left to crystallise; on recrystallisation from methanol the mercaptide was obtained as colourless crystals, m. p. 71° (Found: S, 14.9; Hg, 46.4. $C_{12}H_{22}S_2Hg$ requires S, 14.9; Hg, 46.4%). The redistilled sulphide was a colourless liquid, b. p. 74°/0.2 mm., n_D^{20} 1.5162 (Found: C, 72.5; H, 11.1; S, 16.2. Calc. for $C_{12}H_{22}S$: C, 72.7; H, 11.1; S, 16.2%). and the disulphide a pale yellow liquid b. p. 110–112°/0.2 mm., n_D^{20} 1.5557 (Found: C, 63.0; H, 9.7; S, 27.4. Calc. for $C_{12}H_{20}S_2$: C, 62.7; H, 9.6; S, 27.8%). On standing with methyl iodide the monosulphide yielded a yellow oil which slowly solidified to the *methiodide* of dicyclohexyl sulphide; recrystallisation from ether containing a little alcohol gave colourless crystals, m. p. 110–111° (Found: I, 37.4. $C_{12}H_{22}SI$ requires I, 37.2%). This m. p. is the same as that obtained by Meyer and Hohenemser for the *methiodide* derived from the partly unsaturated sulphide (*Helv. Chim. Acta*, 1935, 18, 1061).

Dihydromyrcene.—Myrcene, prepared from bay oil (*Pimenta acris*) by the method of Power and Kleber (*Pharm. Rundschau*, 1895, 13, 60), was reduced with sodium and alcohol as described by Semmler and Mayer (*Ber.*, 1911, 44, 2010). The hydrocarbon, after being twice fractionally distilled over sodium, had b. p. 60°/16 mm., n_D^{20} 1.4542 (Found: C, 87.2; H, 12.9. Calc. for $C_{10}H_{18}$: C, 87.0; H, 13.0%).

Dihydromyrcene and Hydrogen Sulphide (Sulphur Catalyst).—A mixture of dihydromyrcene (69 g.), hydrogen sulphide (38 g.), and sulphur (0.5 g.) was heated in the autoclave for 20 hours at ca. 130°. On fractionation of the product the b. p. rose steadily from 50 to 90°/9 mm. and then from 68° to 80°/1 mm.; apart from unchanged dihydromyrcene, the distillate contained a mixture of isomeric monothiois, cyclic monosulphide (ca. 11 g.), and cyclic disulphide (2 g.), and a polymeric residue (1 g.) remained. The distillate fractions were extracted with 10% aqueous alkali in absence of air, and the extract after acidification was extracted with ether. Only a drop of liquid was thus obtained, but its odour was definitely mercaptan-like. Fractional distillation of the sulphide fractions gave a mixture of the $C_{10}H_{20}S$ isomers, (IV), (V), and (VI), b. p. 83°/9 mm., n_D^{20} 1.4858 (Found: C, 69.9; H, 11.4; S, 18.6. Calc. for $C_{10}H_{20}S$: C, 69.8; H, 11.6; S, 18.6%). With methyl iodide this product gave an oil, which on long standing yielded yellow crystals of the *methiodide*, m. p. 126–127° (decomp.) in insufficient quantity for complete purification (Found: I, 39.1. $C_{11}H_{22}I$ requires I, 40.3%). No pure disulphide was isolable but it was present to large extent in the higher fractions, such as one, b. p. 70°/1 mm., n_D^{20} 1.5202 (Found: C, 60.7; H, 10.0; S, 28.6. $C_{10}H_{20}S_2$ requires C, 58.8; H, 9.8; S, 31.3%).

A similar reaction between dihydromyrcene and hydrogen sulphide in the presence of sulphur, conducted at 160° for 22 hours, gave a product containing the $C_{10}H_{20}S$ isomers (15 g.), disulphide (3 g.), and polymeric compounds (1.5 g.).

The combined hydrocarbon fractions from the above experiments were again extracted with alkali, washed with water, dried (K_2CO_3), and distilled through a Fenske column. The recovered dihydromyrcene had b. p. 60°/16 mm., n_D^{20} 1.4511, and was shown by analytical and absorption-spectra measurements not appreciably to have cyclised or isomerised (Found: C, 87.2; H, 12.9; I.V., 362. Calc. for $C_{10}H_{18}$: C, 87.0; H, 13.0%; I.V., 368).

Geraniolene.—Citral was oxidised with silver oxide (Bernhauer and Forster, *J. pr. Chem.*, 1936, 147, 199), and the resulting geranic acid was decarboxylated at 260–270° (Tiemann and Semmler, *Ber.*,

1893, 26, 2724) to give geraniolene, b. p. $36^{\circ}/10$ mm., n_D^{20} 1.4408 (Found: C, 87.0; H, 12.9; I.V., 385. Calc. for $C_{10}H_{16}$: C, 87.1; H, 12.9%; I.V. 409). The low I.V. indicated the presence of some cyclised isomer.

Geraniolene and Hydrogen Sulphide (Sulphur Catalyst).—A mixture of geraniolene (70 g.), hydrogen sulphide (45 g.), and sulphur (0.5 g.) was heated in the autoclave for 24 hours at 150° . Distillation of the product gave a mixture of isomeric monothiol and cyclic monosulphide (12.5 g.), disulphide (1 g.), and a polymeric residue (1.5 g.). From the monosulphide fraction was obtained a pure mixture of the $C_{10}H_{16}S$ isomers (VII), (VIII), and (IX), b. p. $87^{\circ}/16$ mm., n_D^{20} 1.4812 (Found: C, 68.2; H, 11.4; S, 20.2%. Calc. for $C_{10}H_{16}S$: C, 68.4; H, 11.4; S, 20.2%). Reaction of this product with methyl iodide at 15° gave an oil which would not solidify. The fraction containing the highest percentage of disulphide had b. p. $75^{\circ}/1$ mm., n_D^{20} 1.5100 (Found: C, 59.0; H, 10.1; S, 29.3. $C_{10}H_{16}S_2$ requires C, 58.9; H, 9.5; S, 33.7%).

Geraniolene and Hydrogen Sulphide (Aluminium Sulphide Catalyst).—A mixture of geraniolene (42 g.), recovered from the foregoing experiment), hydrogen sulphide (38 g.), aluminium sulphide (6 g.), and quinol (2 g.) was heated in the autoclave in the absence of air for 26 hours at ca. 150° . The product in ethereal solution was thoroughly extracted with 10% aqueous sodium hydroxide, washed with water, and dried (Na_2SO_4). On exposure to air the alkaline extract immediately started oxidising, with the formation of a viscous red oil (evidently a polymeric disulphide). Fractional distillation of the ethereal extract gave the $C_{10}H_{16}S$ isomeric mixture (5.2 g.), with b. p. ranging from 69 – $71^{\circ}/11$ mm., n_D^{20} 1.4729 (Found: C, 68.5; H, 11.2; S, 19.9; $\cdot SH$, 8.7%), to 80 – $81^{\circ}/11$ mm., n_D^{20} 1.4778 (Found: C, 67.9; H, 11.4; S, 20.3; $\cdot SH$, 12.3. Calc. for $C_{10}H_{16}S$: C, 68.4; H, 11.4; S, 20.2; $\cdot SH$, 0%). Calc. for $C_{10}H_{16}\cdot SH$: $\cdot SH$, 20.9%). No disulphide was isolable, although one fraction (1.0 g.) contained a small proportion thereof (Found: S, 22.1. Calc. for $C_{10}H_{16}S$: S, 20.2. Calc. for $C_{10}H_{16}S_2$: S, 33.6%). An intermolecular sulphide fraction (0.5 g.), b. p. 117 – $122^{\circ}/0.5$ mm., n_D^{20} 1.4988, was isolated, and it appeared to be mainly the compound $C_{10}H_{16}S\cdot C_{10}H_{16}\cdot SH$ (see p. 1539) containing some $C_{10}H_{16}\cdot S\cdot C_{10}H_{16}$ (Found: C, 70.0; H, 11.1; S, 18.7. Calc. for $C_{10}H_{16}S_2$: C, 68.4; H, 11.4; S, 20.2%. Calc. for $C_{10}H_{16}S_2$: C, 76.6; H, 12.0; S, 11.3%).

Separation of the $C_{10}H_{16}S$ isomers. An approximately 0.2N-solution of cupric butyl phthalate (Turk and Reid, *loc. cit.*) was prepared by dissolving the reagent (5.1 g.) in 100 ml. of *n*-propyl alcohol containing acetic acid (5 ml.). This reagent was introduced into a solution of the $C_{10}H_{16}S$ mixture (3.3 g.) in *n*-propyl alcohol (50 ml.) until the green colour just persisted. After dilution with water to 800 ml. the product was extracted with chloroform, washed with water, dried, and fractionally distilled. After refractionation, 2:2:6-tetramethyltetrahydrothiopyran (IX) (1 g.) was obtained as a colourless liquid, b. p. 64 – $66^{\circ}/11$ mm., n_D^{20} 1.4732 (Found: C, 68.4; H, 11.3; S, 19.9. Calc. for $C_{10}H_{16}S$: C, 68.4; H, 11.4; S, 20.2%).

Reaction of (IX) with methyl iodide at 0° gave only an oil, but when the sulphide was heated with excess of methyl iodide at 100° for 12 hours, yellow crystals separated, which after being washed with methanol and recrystallised from ethanol decomposed at ca. 200° and proved to be trimethylsulphonium iodide (Found: S, 15.7; I, 61.9. Calc. for C_3H_9SI : S, 15.7; I, 62.2%).

2:6-Dimethylocta-2:6-diene.—Geraniol was purified by conversion into its calcium chloride compound, and then reduced by sodium in liquid ammonia (Chablay; Dupont, Dulou, and Desreux, *loc. cit.*). After fractional distillation over sodium, the pure hydrocarbon had b. p. $56^{\circ}/14$ mm., n_D^{20} 1.4517 (Found: C, 87.0; H, 13.2; I.V., 370. Calc. for $C_{10}H_{18}$: C, 87.0; H, 13.0%; I.V., 368).

2:6-Dimethylocta-2:6-diene and Hydrogen Sulphide (Normal Addition).—A mixture of the olefin (69 g.), hydrogen sulphide (38 g.), and sulphur (0.5 g.) was heated in absence of oxygen under pressure for 22 hours at 140 – 150° . After extraction with aqueous alkali, fractional distillation of the product gave a mixture of $C_{10}H_{16}S$ isomers (5 g.) and a higher-boiling fraction which in this instance was not separated. Refractionation of the former yielded the $C_{10}H_{16}S$ isomers, b. p. 92 – $94^{\circ}/18$ mm., n_D^{20} 1.4842 (Found: C, 69.8; H, 11.5; S, 18.3. Calc. for $C_{10}H_{16}S$: C, 69.8; H, 11.6; S, 18.6%); this fraction contained about 11% of the monothiol (Found: $\cdot SH$, 2.1. Calc. for $C_{10}H_{16}\cdot SH$: $\cdot SH$, 19.2%). The unreacted olefin was recovered and shown to be uncyclised 2:6-dimethylocta-2:6-diene, b. p. $54^{\circ}/13$ mm., n_D^{20} 1.4501 (Found: C, 87.0; H, 13.2; I.V., 370. Calc. for $C_{10}H_{18}$: C, 87.0; H, 13.0%; I.V., 368).

In a further similar experiment 2:6-dimethylocta-2:6-diene (92 g.) was treated with hydrogen sulphide (58 g.) in the presence of aluminium sulphide (10 g.) for 23 hours at 150 – 165° . After extraction with 10% aqueous sodium hydroxide solution, the product was distilled as before to give the $C_{10}H_{16}S$ fraction (11 g.), b. p. ca. 76 – $89^{\circ}/9$ mm.), disulphide (0.5 g., not isolable), and a residue of intermolecular sulphides (0.5 g.). On refractionation of the $C_{10}H_{16}S$ fraction, a product was obtained, b. p. 87 – 88° , n_D^{20} 1.4798 (Found: C, 69.6; H, 11.6; S, 18.6. Calc. for $C_{10}H_{16}S$: C, 69.8; H, 11.6; S, 18.6%), which contained ca. 27% of the monothiol 2(or 6)-mercapto-2:6-dimethyloct-6(or 2)-ene (Found: $\cdot SH$, 5.1. Calc. for $C_{10}H_{16}\cdot SH$: $\cdot SH$, 19.2%). Treatment of this product with copper butyl phthalate, in a manner analogous to that used for separation of the $C_{10}H_{16}S$ isomers, led to the isolation of 2:2:6-trimethyl-6-ethyl-tetrahydrothiopyran, b. p. $84^{\circ}/10$ mm., n_D^{20} 1.4792 (Found: C, 69.4; H, 11.5; S, 18.3. Calc. for $C_{10}H_{16}S$: C, 69.8; H, 11.6; S, 18.6%). Reaction with methyl iodide at 0 – 15° gave an oil which crystallised only extremely slowly, and reaction at 100° gave trimethylsulphonium iodide (Found: S, 15.7; I, 61.9. Calc. for C_3H_9SI : S, 15.7; I, 62.2%). By acidification of the alkali extract and subsequent extraction with ether was obtained 2:6-dimercapto-2:6-dimethyloctane (0.5 g.), b. p. $110^{\circ}/9$ mm., n_D^{20} 1.4971 (Found: C, 58.2; H, 10.6; S, 31.0; $\cdot SH$, 32.0. $C_{10}H_{16}S_2$ requires C, 58.3; H, 10.7; S, 31.0; $\cdot SH$, 32.0%).

In a third experiment a mixture of 2:6-dimethylocta-2:6-diene (77 g.), hydrogen sulphide (48 g.), aluminium sulphide (8 g.), and quinol (2 g.) was heated for 24 hours at ca. 150° . From the $C_{10}H_{16}S$ fraction (7.5 g.) was obtained a mixture of isomers, b. p. 86 – $8^{\circ}/10$ mm., n_D^{20} 1.4782 (Found: C, 69.7; H, 11.5; S, 18.7. Calc. for $C_{10}H_{16}S$: C, 69.8; H, 11.6; S, 18.6%), which contained 42% of the monothiol (Found: $\cdot SH$, 8.0. Calc. for $C_{10}H_{16}\cdot SH$: $\cdot SH$, 19.2%). Removal of the latter by the copper butyl phthalate method left somewhat impure 2:2:6-trimethyl-6-ethyl-tetrahydrothiopyran, b. p. 80 – $83^{\circ}/11$ mm., n_D^{20} 1.4806 (Found: C, 70.7; H, 11.6; S, 17.5. Calc. for $C_{10}H_{16}S$: C, 69.8; H, 11.6; S, 18.6%).

2:6-Dimethylocta-2:6-diene and Hydrogen Sulphide (Abnormal Addition).—Two Pyrex tubes, each containing the olefin (18.3 g.), hydrogen sulphide (5.1 g.), and acetone (1.2 g.), were sealed under vacuum and irradiated with U.V. light at 15° for 4 hours. After extraction with 10% aqueous alkali, the product was fractionally distilled to give a $C_{10}H_{18}S$ isomeric mixture (9 g.) and intermolecular sulphides (2 g.). From the former was obtained a fraction, b. p. 92–92.5°/11 mm., n_D^{20} 1.4767 (Found: C, 69.8; H, 11.6; S, 18.6. Calc. for $C_{10}H_{18}S$ requires C, 69.8; H, 11.6; S, 18.6%), which contained 56% of the monothiol, 3(or 7)-mercapto-2:6-dimethyloct-6(or 3)-ene (Found: $\cdot SH$, 10.8. $C_{10}H_{18}\cdot SH$ requires $\cdot SH$, 19.2%). Removal of the thiol by the copper butyl phthalate method left 2:3-dimethyl-6-isopropyl-tetrahydrothiopyran, b. p. 46°/1 mm., n_D^{20} 1.4831 (Found: C, 69.7; H, 11.5; S, 18.2. $C_{10}H_{18}S$ requires C, 69.8; H, 11.6; S, 18.6%). Acidification of the alkaline extract liberated 3:7-dimercapto-2:6-dimethyloctane, b. p. 132°/11 mm., n_D^{20} 1.5025 (Found: C, 58.3; H, 11.0; S, 30.8. $C_{10}H_{18}S_2$ requires C, 58.3; H, 10.7; S, 31.0%). Fractionation of the intermolecular sulphide fraction led to the separation of 5(or 2)-mercapto-1:2:6-trimethylheptyl 4-methyl-1-isopropylhex-4-enyl sulphide or the 1:5-dimethyl-1-ethylhex-4-enyl sulphide (as XV), b. p. 147°/0.1 mm., n_D^{20} 1.4990 (Found: C, 69.4; H, 11.6; S, 18.8; $\cdot SH$, 10.0. $C_{10}H_{18}S$ requires C, 69.8; H, 11.6; S, 18.6; $\cdot SH$, 9.6%).

Nitrous Acid Test for Thiols.—Dilute sulphuric acid was slowly added to an alcoholic solution of the thiol containing solid sodium nitrite, through which nitrogen was bubbling (Rheinboldt, *loc. cit.*). All the products of normal addition of hydrogen sulphide to dihydromyrcene and 2:6-dimethylocta-2:6-diene gave green oils which appeared red in bulk when viewed by transmitted light; this was indicative of the tertiary grouping $CRR'R''SH$. The U.V.-light-catalysed reaction product gave a bright red oil indicating the secondary grouping $CHRR'SH$ (the formation of a primary thiol not being feasible in this reaction), and the geraniolene products a reddish oil, which pointed to the presence of at least some secondary thiol.

Rubber and Hydrogen Sulphide (Abnormal Addition).—A 1% benzene solution of sol rubber was shaken with hydrogen sulphide in absence of air, and irradiated in a quartz flask with ultra-violet light for 4 hours. The product after separation by precipitation with alcohol and drying in a high vacuum contained 1.1% of sulphur. The experiment was repeated using as solvent benzene containing 5% of acetone as photosensitiser. From two runs the products contained 2.25 and 2.65% of sulphur severally; a very small quantity of rubber came out of solution as a gel, and in the latter case this contained 10.1% of sulphur. When crepe containing its natural antioxidants was used, the sulphur value obtained was 0.8%. Seven hours' irradiation of a 9% solution of milled acetone-extracted crepe in benzene containing 5% of acetone gave small quantities of gels containing 4.5–2.2% of sulphur, and a main product with 1% (M , 153,000). The same conditions, 1% solutions being used without irradiation, led to incorporation of only 0.15% of sulphur. A further solution was saturated with hydrogen sulphide at 0° and then heated with benzoyl peroxide for 1 hour at 75°; this increased the sulphur intake to 0.30%.

Milled acetone-extracted crepe (0.5 g.) and liquid hydrogen sulphide (30 ml.) were sealed in a Pyrex tube. After 3 days with occasional gentle shaking the rubber passed into solution, and was then irradiated for 25 minutes at 15°; the product contained 2.07% of sulphur. On repetition of the experiment with milled crepe (0.7 g.), hydrogen sulphide (24 ml.), and acetone (1.2 ml.), the rubber did not go wholly into solution. The analyses of the two portions after 25 minutes irradiation were: Found, for insoluble fraction, C, 85.6; H, 11.6; S, 1.3; ash, 0.17; O (diff.), 1.3%. Found, for soluble fraction, C, 85.0; H, 11.65; S, 3.2; ash, 0.09; O (diff.), 0.06%. It is evident that liquid hydrogen sulphide preferentially dissolved the pure hydrocarbon, as the starting material contained 1.0% of oxygen.

Rubber and Hydrogen Sulphide (Normal Addition).—Similar 1-mm. sheets (10 g.) of crepe rubber, milled alone and with $\frac{1}{4}$ % of sulphur, were heated with hydrogen sulphide (24 g.) in the autoclave in absence of air for 2 hours at 140°. The products, although full of small hydrogen sulphide bubbles, were elastic like sulphur-vulcanised rubber (Found, for uncatalysed product: S, 1.9; 2.2. For catalysed product: S, 2.7; 2.8%). After a similar reaction at 140–160° the products were acetone-extracted to remove free sulphur (Found, for uncatalysed product: S, 2.75. For catalysed product: S, 3.25%); at this temperature acetone-extracted crepe rubber reacted to give a product (Found: S, 3.15%) after further acetone-extraction. Reaction of milled crepe (10 g.) with hydrogen sulphide (24 g.) for 2 hours at 260° yielded a product in which some chain fission had obviously taken place (Found: S, 8.5%). Sheets of milled crepe with and without $\frac{1}{4}$ % of sulphur were heated at 140° for 48 hours in hydrogen sulphide at atmospheric pressure (Found, for uncatalysed product: S, 0.5; for catalysed product, S, 0.8%); a control sample heated in nitrogen was unchanged.

An 8% solution (250 ml.) of milled acetone-extracted crepe rubber in cyclohexane, liquid hydrogen sulphide (60 g.), ferrous sulphide (4 g.), and ferric oxide (2 g.) were sealed in the autoclave in absence of air and heated for 20 hours at 85–103°. Some rubber (3–4 g.) came out of solution as a gel (Found: S, 4.8%). The main solution was centrifuged to remove catalyst, and the rubber precipitated by alcohol (Found: S, 1.1%).

This paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The author wishes to express his thanks to Dr. E. H. Farmer for his advice and criticism, to Dr. G. B. M. Sutherland and Mr. N. Sheppard for examination of the infra-red absorption spectra and for valuable discussions on their inference, and to Dr. G. Gee for the molecular-weight determinations.

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[Received, January 15th, 1947.]

300. *The Application of Infra-red Analysis to the Study of the Reaction of Certain Olefins with Hydrogen Sulphide.*

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The method of infra-red analysis has been used to investigate the reaction of geraniolene and dihydromyrcene with hydrogen sulphide in the presence of catalysts that usually promote "normal" addition to the double bond according to the Markovnikov rule. It has been possible to show conclusively that under these conditions both the hydrocarbons give mono-addition products which consist partly of cyclic sulphides, geraniolene giving rise to 2 : 2 : 6 : 6-tetramethyltetrahydrothiopyran, and dihydromyrcene to 2 : 2 : 6-trimethyl-6-ethyltetrahydrothiopyran. Such products could only have been formed by "normal" addition reactions. The products of the reaction of hydrogen sulphide with dihydromyrcene under conditions favouring "abnormal" addition gave very different spectra.

In order to apply the infra-red method it was necessary first to establish rules for the spectroscopic identification of certain hydrocarbon groups. These rules are briefly discussed.

IN the preceding paper Naylor has described an investigation of the reaction of hydrogen sulphide with the hydrocarbons geraniolene and dihydromyrcene. Many of the conclusions relating to the structures of the reaction products came from an investigation of their infra-red spectra. The purpose of this paper is to present in detail the evidence for these conclusions.

Infra-red analysis can be used in two ways to establish the structure of a reaction product. In the first place, any chemical bond or group that has characteristic infra-red absorption bands can be detected, and while in most cases this does not establish the structure it may enable one to eliminate some of the possible formulations and give strong presumptive evidence for a particular one. The second and more conclusive method is to compare the spectrum of the reaction product with that of a specially synthesised specimen of the compound postulated as the reaction product. Both methods have been used in the present investigation, the first two sections of which are concerned with the material required for the first method, while the third contains the combined application of both methods to the problem in hand.

Chemical Groupings and their Characteristic Absorption Bands.—The various characteristic group frequencies that we shall use in the examination of the reaction products are given in Table I, where R represents an alkyl group. Most of these correlations are well established

TABLE I.

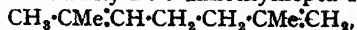
Chemical grouping.	Type of vibration.	Frequency in cm^{-1} .
SH	SH valence	2500—2650
CH_2 and CH_3	CH deformation	1430—1470
CH_3	CH deformation	1370—1375
$\text{C} \begin{smallmatrix} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{smallmatrix}$	CH deformation	ca. 1360 and 1380 *
$\text{RR}'\text{C}:\text{CH}_2$	$\text{C}=\text{C}$ valence	1645—1655 *
$\text{RR}'\text{C}:\text{CH}$	CH deformation	885—895
$\text{RR}'\text{C}:\text{CHR}''$	$\text{C}=\text{C}$ valence	1670—1680 *
$\text{RR}'\text{C}:\text{CHR}''$	CH deformation	800—840

(see, e.g., Herzberg, "Infra-red and Raman Spectra of Polyatomic Molecules," Van Nostrand Co. Inc., 1946; Barnes, Gore, Liddel, and Williams, "Infra-red Spectroscopy," Reinhold, 1944; Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246), but those marked with an asterisk, which are more precise characterisations of older correlations, have recently been established in this laboratory and full details will be published elsewhere.

Both the $\text{C}=\text{C}$ valence and the $\text{C}-\text{H}$ deformation absorptions of the disubstituted ethylenes have considerably higher extinction coefficients than the corresponding absorptions of the trisubstituted compounds. This is important if such absorptions are used to estimate the relative amounts of the two types of grouping in a mixture of both.

The Spectra of the Olefins.—The two hydrocarbons originally used for the reaction with hydrogen sulphide were geraniolene and dihydromyrcene. Their spectra are shown in Fig. 1, and in this and the subsequent figures absorption bands mentioned in the text are accented by a line down the middle in the appropriate spectra.

Geraniolene is considered to be mainly 2 : 6-dimethylhepta-1 : 5-diene,



although its method of preparation (Bernhauer high-temperature decarboxylation; see Naylor, *loc. cit.*) does not exclude the possibility of considerable amounts of other isomers. Its infra-red spectrum has absorption bands at 1654 and 891 cm^{-1} , and at 1680 and 821 cm^{-1} which

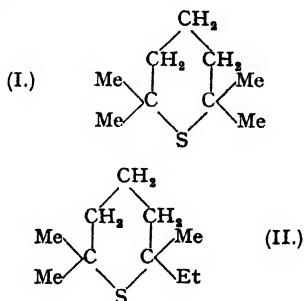
can be ascribed to $C=C$ valence and $C-H$ deformation vibrations respectively of $RR'C:CH_2$ and $RR'C:CHR''$ groups, in agreement with the above formula (see Table I).

Dihydromyrcene is generally assumed to consist largely of 2:6-dimethylocta-2:6-diene, $CH_3 \cdot CMe:CH \cdot CH_2 \cdot CH_2 \cdot CMe:CH \cdot CH_3$, but its method of preparation (Naylor, *loc. cit.*) suggests that the isomers 2:6-dimethylocta-1:6-diene, $CH_3 \cdot CMe:CH_2 \cdot CH_2 \cdot CH_2 \cdot CMe:CH \cdot CH_3$, and 6-methyl-2-ethylhepta-1:5-diene,

$CH_3 \cdot CMe:CH \cdot CH_2 \cdot CH_2 \cdot CEt:CH_2$, may also be present. Comparison of the spectrum of this material with that of pure 2:6-dimethylocta-2:6-diene, prepared by an independent method, shows that in addition to the usual bands attributable to the $RR'C:CHR''$ groups (at 1678 and 820 cm^{-1}) there are also bands (at 1650 and 889 cm^{-1}) attributable to the $RR'C:CH_2$ groups of these alternative isomers. For this reason the dihydromyrcene used in the earlier experiments with hydrogen sulphide and sulphur catalyst was subsequently replaced by the pure 2:6-dimethylocta-2:6-diene.

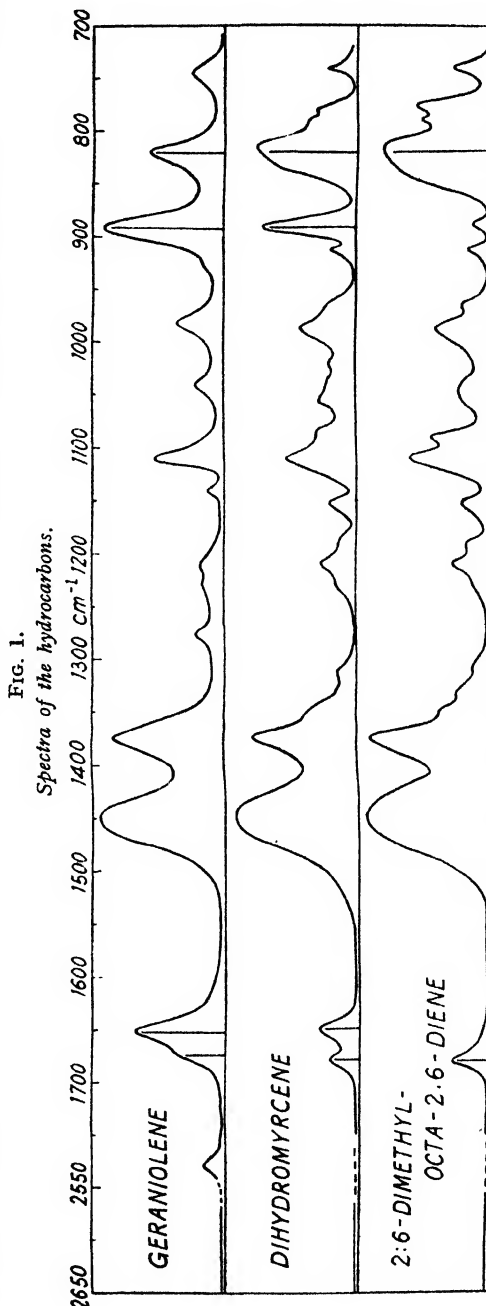
Infra-red Analysis of the Reaction Products.—

(1) *General.* The chemical aspects of the reactions of geraniolene and dihydromyrcene with hydrogen sulphide have been fully discussed by Naylor (*loc. cit.*). The spectroscopic problem was to investigate certain portions of the products obtained with catalysts that promote "normal" addition according to the Markovnikov rule. In particular we required to establish the presence or absence of 2:2:6:6-tetramethyltetrahydrothiopyran (I) and 2:2:6-trimethyl-6-ethyltetrahydrothiopyran (II) as reaction products of the respective hydrocarbons.

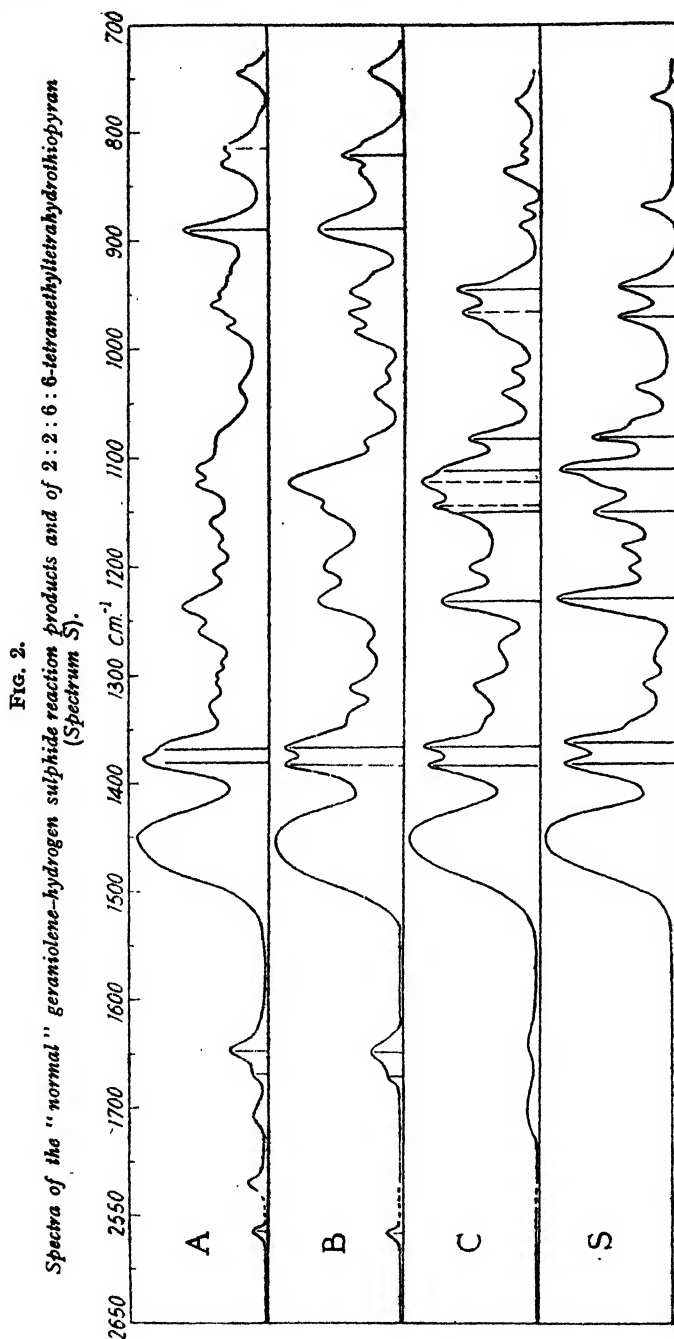


We also investigated some products from similar reactions in which the conditions were such that products of "abnormal" addition were to be expected.

The spectra of the reaction products of geraniolene and hydrogen sulphide obtained under conditions of normal addition are given in Fig. 2, the steps in the gradual purification and identification being indicated by the following key: (A) Spectrum of the reaction product, sulphur being used as catalyst. (B) Spectrum of the reaction product, aluminium sulphide being used as catalyst (to avoid the possibility of the catalyst reacting with the hydrocarbon). (C) Spectrum of B after removal

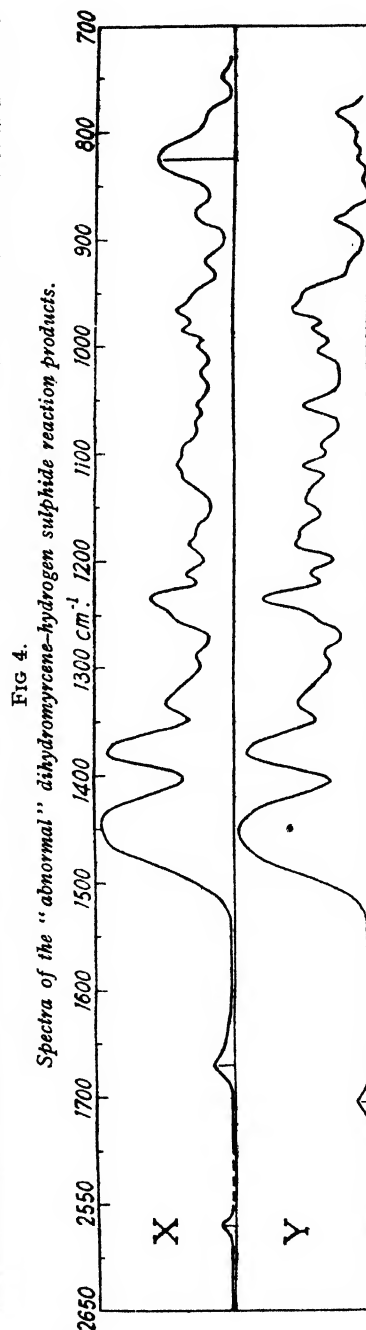
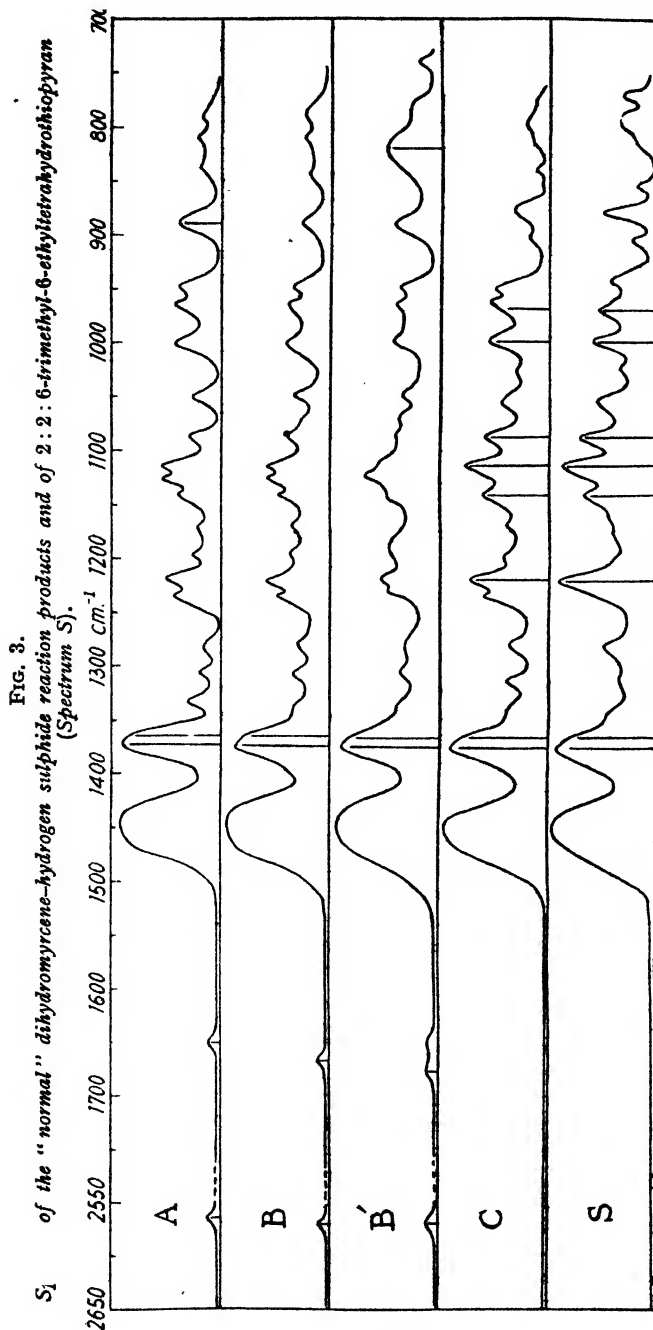


of thiols by cupric butyl phthalate. (S) Spectrum of synthetic 2:2:6:6-tetramethyltetrahydrothiopyran.



The corresponding spectra for the dihydromyrcene reaction are given in Fig. 3, but it should be noted that only (A) refers to the reaction with dihydromyrcene; the remaining spectra are all of products obtained by using the synthetic specimen of the single isomer 2:6-dimethylocta-2:6-diene of which the spectrum is given in Fig. 1. It should also be noted that (B') of Fig. 3 is the spectrum of a reaction product obtained under the same conditions as (B) but

with some quinol present to remove any peroxides. As in the case of the geraniolene products, (C) and (S) denote respectively the thiol-free product and the independently synthesised cyclic sulphide.



In Fig. 4 are represented the spectra of the products obtained when 2:6-dimethylocta-2:6-diene and hydrogen sulphide are irradiated with ultra-violet light—conditions that should promote abnormal addition: (X) is the original unpurified product, and (Y) the thiol-free material.

(2) *The products of the geraniolene-hydrogen sulphide reaction under "normal" conditions* (see Fig. 2). The expected product—2:2:6:6-tetramethyltetrahydrothiopyran—has four methyl groups that occur in pairs, and this should give rise to the splitting of the 1370 cm^{-1} band. Such a splitting (1381 and 1362 cm^{-1}) is found in the spectrum of the synthetic material (S), and confirms its authenticity. Other bands in the spectrum of (S) which can be used for the identification of this sulphide in the reaction product occur at 1229, 1149, 1111, 1079, 971, and 942 cm^{-1} .

Product A (sulphur as catalyst) has a poorly defined spectrum which shows little splitting of the 1370 cm^{-1} band, and in addition has absorptions at 1648 and 889 cm^{-1} characteristic of $\text{RR}'\text{C}:\text{CH}_2$ groupings, 1670 and 815 cm^{-1} characteristic of $\text{RR}'\text{C}:\text{CHR}''$ groupings, and 2570 cm^{-1} caused by SH groups. In other words, it is obvious that further purification was necessary, and that at least some of the impurities were residual amounts of monothiol.

The aluminium sulphide-catalysed product (B) has a cleaner spectrum—due probably to the absence of any sulphur-geraniolene products—but still retains the other groupings corresponding to the monothiol. However, after removal of these by cupric butyl phthalate (product C) a fairly clean spectrum is obtained with, as required, a pronounced splitting of the 1370 cm^{-1} band (1381 and 1363 cm^{-1}). In addition, the strong bands which occur at 1231, 1150, 1111, 1082, and 945 cm^{-1} show that there is a considerable amount of the expected sulphide present. Several well-pronounced bands remain, however, which are not due to the expected product, and one of these obscures the 971 cm^{-1} position. The three strongest bands which cannot be attributed to this sulphide have their centres at 1144, 1122, and 965 cm^{-1} , all of which are very close to strong absorptions of the synthesised cyclic sulphide.

(3) *The products of the dihydromyrcene-hydrogen sulphide reaction under "normal" conditions* (see Fig. 3). The spectrum of the specially synthesised 2:2:6-trimethyl-6-ethyltetrahydrothiopyran (S) has absorptions at 1220, 1142, 1116, 1087, 1002, 970 cm^{-1} which can be used for identification purposes. In this case the splitting of the 1370 cm^{-1} band is only just detectable, as is to be expected, since there are equal numbers of "paired" and "lone" methyl groups present. It is interesting to note a strong general resemblance between this spectrum and that of 2:2:6:6-tetramethyltetrahydrothiopyran, and this correspondence confirms the closely related structures of these two substances.

Product A (sulphur as catalyst) gives the spectrum shown at the top of Fig. 3. A small proportion of SH groups is indicated by the usual band at 2570 cm^{-1} , and also some unsaturation of the disubstituted type $\text{RR}'\text{C}:\text{CH}_2$ by the bands at 1650 and 889 cm^{-1} . The fact that some of the residual unsaturation is of the disubstituted type in this case is surprising in view of the fact that the initial hydrocarbon should have few such groupings. However, product B (with pure 2,6-dimethylocta-2:6-diene and aluminium sulphide as catalyst) does not show any considerable absorptions in these positions, and the probability that this disubstituted unsaturation is due to some sulphur-dihydromyrcene reaction products is substantiated by the presence of bands at 1650 and 890 cm^{-1} in the spectra of such products (unpublished work). Very weak bands at 2570 cm^{-1} and *ca.* 1660–1670 cm^{-1} suggest that there is some residue including thiol. Product B' (obtained as B but with quinol present) has a considerable number of SH and unsaturated groupings—the latter being predominantly of the trisubstituted type (1680 and 820 cm^{-1}). Otherwise its spectrum is very similar to that of B, indicating that the removal of any peroxides that might have been present during the reaction had little effect on the product. This is additional evidence that it is not formed by "abnormal" addition.

Finally, the removal of thiol from (B) by cupric butyl phthalate (product C) caused the disappearance of SH and unsaturation absorptions. The resultant material gives a reasonably clean spectrum. Comparison of this spectrum (C) with that of the synthesised material (S) which was taken with the same path-length of liquid, shows that all the characteristic bands of 2:2:6-trimethyl-6-ethyltetrahydrothiopyran are present in strength comparable with those of the pure material. One or two weak additional bands are present in (C) which presumably correspond to a small amount of impurity, but the product is very nearly all pure sulphide of the expected type.

(4) *The products of the dihydromyrcene-hydrogen sulphide reaction under "abnormal" conditions* (see Fig. 4). The product (X) was formed by the ultra-violet-catalysed reaction between pure 2:6-dimethylocta-2:6-diene and hydrogen sulphide and would be expected to be "abnormal" in type. It has a very different spectrum from those products discussed in the preceding section although it does have bands at 2580 cm^{-1} (SH groups) and at 1670 and 825 cm^{-1} characteristic of trisubstituted double bonds. This means that there is a considerable proportion of monothiol present. Removal of this by the usual method gave product

(Y), which has a spectrum similar to (X) except that the above three bands have disappeared. There remains a weak band near 1700 cm^{-1} which is probably due to some impurity introduced during the removal of thiol, as such a frequency is characteristic of C=O rather than $\text{C}\equiv\text{C}$ groups. The spectrum of this sample is completely different from that of the final "normal" product of Section (3).

DISCUSSION.

We have shown that the spectra of the reaction products under conditions favouring "normal" addition are extremely similar to those of 2:2:6:6-tetramethyl- and 2:2:6-trimethyl-6-ethyl-tetrahydrothiopyran, but there are certain discrepancies which must be considered before this strong resemblance can be accepted as conclusive proof of the identities of the reaction products. When spectra differ in this way it may be either because impurities are present, or because the compounds of which the spectra are being compared are really different, but of closely related structure. These two cases, which we shall call (1) and (2), can usually be distinguished. In the former, the main bands of the pure compound should be stronger than the corresponding bands in the unknown for the same cell thickness, unless, of course, a band due to the impurity overlaps one of these "key" bands. From Figs. 2 and 3 it will be seen that this is indeed the case for our comparisons. Again, in case (1) all bands, except the very weakest, detectable in the spectrum of the pure compound should be present in the unknown, whereas in case (2) the number of weak bands may be greater for the pure compound than the unknown. It will be seen that on this criterion also our identification is justified, for although there is one weak band in 2:2:6:6-tetramethyltetrahydrothiopyran (near 1180 cm^{-1}) which does not appear in the (C) spectrum (Fig. 2), this sole exception may well be due to a trace of impurity in the synthetic compound.

In the case of the comparison of the geraniolene product with the synthetic 2:2:6:6-tetramethyltetrahydrothiopyran, it is obvious that the amount of "impurity" is considerable and it is thought that this arises from the presence of other isomers than 2:6-dimethylhepta-1:5-diene in the original hydrocarbon. The dihydromyrcene product has relatively little impurity, in agreement with the fact that pure 2:6-dimethylocta-2:6-diene was used for the reaction.

We wish to draw attention in this connection to the power of the infra-red method in detecting by-products in a reaction. The difficulty of sufficiently purifying the product to enable us to use infra-red analysis is a sufficient indication of this, and of the precision of the identification once that purification has been achieved.

EXPERIMENTAL.

The infra-red spectra were taken with the Hilger Double-Beam Spectrometer described by Sutherland and Thompson (*Trans. Faraday Soc.*, 1945, **41**, 174). They were recorded under double-beam conditions so that the absorption of radiation by water vapour in the atmosphere did not interfere with the spectra.

TABLE II.

Analytical data for the samples investigated spectroscopically.

Compound.	B. p.	Refractive index.	Found, %.			Calculated, %.		
			C.	H.	S.	C.	H.	S.
Geraniolene	$36^{\circ}/10\text{ mm.}$	$n_D^{18} 1.4408$	87.0	12.9	—	87.1	12.9	—
Dihydromyrcene.....	$60/16\text{ mm.}$	$n_D^{18} 1.4542$	87.2	12.9	—	87.0	13.0	—
2:6-Dimethylocta-2:6-diene	$56/14\text{ mm.}$	$n_D^{17} 1.4517$	87.0	13.2	—	87.0	13.0	—
Geraniolene products A ...	$86-87/16\text{ mm.}$	$n_D^{18} 1.4812$	68.2	11.4	20.2	68.4	11.4	20.2
" " B ...	$69-71/11\text{ mm.}$	$n_D^{18} 1.4729$	68.5	11.2	19.9	"	"	"
" " C ...	$66/11\text{ mm.}$	$n_D^{18} 1.4732$	68.2	11.3	19.9	"	"	"
" " S ...	$66/12\text{ mm.}$	$n_D^{18} 1.4763$	68.3	11.6	20.1	"	"	"
" Normal " dihydromyrcene products A	$83/9\text{ mm.}$	$n_D^{17} 1.4858$	69.9	11.4	18.6	69.8	11.6	18.6
" " B	$87-88/9\text{ mm.}$	$n_D^{18} 1.4798$	69.6	11.6	18.6	"	"	"
" " B'	$86-88/10\text{ mm.}$	$n_D^{20} 1.4782$	69.7	11.5	18.7	"	"	"
" " C	$84/10\text{ mm.}$	$n_D^{18} 1.4792$	69.4	11.5	18.3	"	"	"
" " S	$87/13\text{ mm.}$	$n_D^{20} 1.4849$	69.6	11.7	18.6	"	"	"
" Abnormal " dihydromyrcene products X	$92/11\text{ mm.}$	$n_D^{18} 1.4767$	69.8	11.6	18.6	69.8	11.6	18.6
" " Y	$46/1\text{ mm.}$	$n_D^{16} 1.4831$	69.7	11.5	18.2	"	"	"

1546 Reaction of Sulphur and Sulphur Compounds, etc. Part III.

A rock-salt prism was used throughout for this work, and the effective slit-widths (in cm^{-1}) were 40 at 2000 cm^{-1} , 12 at 1600 cm^{-1} , 8 at 1000 cm^{-1} , and 5 at 700 cm^{-1} . The positions of the bands are accurate to 2 cm^{-1} up to 1300 cm^{-1} , 4 cm^{-1} from 1300 to 1900 cm^{-1} , and 20 cm^{-1} at any higher frequencies in this work.

The experimental details of the olefin-hydrogen sulphide reactions have been given by Naylor (*loc. cit.*) and it will suffice here to give the physical properties and analytical figures for the samples investigated. These figures were obtained by Naylor at Welwyn, and the samples were then sealed in nitrogen and transmitted to Cambridge. The spectra were taken in a rock-salt cell of 0.06 mm. thickness, immediately after the samples had been unsealed.

Our thanks are due to Drs. E. H. Farmer and R. F. Naylor, of the British Rubber Producers' Research Association, for bringing this problem to our notice, and for providing us with all the specimens investigated. We are also grateful to them for much helpful discussion during the course of the work.

One of us (N. S.) is indebted to St. Catharine's College, and the Dunlop Rubber Co. Ltd., for financial help during this investigation. The spectrometer used was provided by a joint grant from the Royal Society and Imperial Chemical Industries Ltd.

LABORATORY OF COLLOID SCIENCE, CAMBRIDGE.

[Received, February 6th, 1947.]

301. The Reaction of Sulphur and Sulphur Compounds with Olefinic Substances. Part III. The Reaction of Sulphur with Squalene.

By GEORGE F. BLOOMFIELD.

Sulphur reacts with squalene in a manner very similar to that observed with dihydromyrcene, and an intramolecularly-linked unimolecular sulphide as well as an intermolecularly-linked polysulphide is obtained.

RATHER prolonged reaction times are necessary to obtain an appreciable degree of sulphuration of squalene, $\text{H}[\text{CH}_2\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2]_3[\text{CH}_2\cdot\text{CH}\cdot\text{CMe}\cdot\text{CH}_2]_3\cdot\text{H}$, below 140° in the absence of auxiliary activating substances, and, as might be expected, the course of the reaction shows a marked resemblance to the sulphuration of dihydromyrcene. The crude reaction product consists of unreacted squalene of undiminished olefinic unsaturation, together with a unimolecular sulphurated product and a bimolecular polysulphide. Of the two sulphurated components, the unimolecular product, which cannot be completely freed from unreacted squalene, is present in the major proportion, although the sulphur which enters into reaction is distributed fairly equally among the two components. The unimolecular product, $\text{C}_{30}\text{H}_{50}\text{S}$, in which one sulphur atom has become incorporated in the squalene molecule with the loss of one double bond, is substantially free from sulphydryl sulphur, and contains carbon and hydrogen in the same ratio as in the original hydrocarbon. The bimolecular product is a polysulphide of squalene, $\text{C}_{60}\text{H}_{100}\text{S}_6$, of considerable stability towards sodium sulphite, and the ratio of hydrogen to carbon is again that of the parent hydrocarbon; the incorporation of sulphur is accompanied by loss of olefinic unsaturation. The unsaturation of the bimolecular product undergoes a further reduction on heating at temperatures exceeding 140° .

In view of the known sensitivity of the reaction of sulphur with olefins towards quite small proportions of certain activating substances, it is of considerable interest that the addition of mercaptobenzthiazole and a zinc soap to the sulphur-squalene system results only in increased yields in both uni- and bi-molecular products without greatly affecting their relative proportions, provided that the time and temperature conditions of the reaction remain unaltered.

EXPERIMENTAL.

Microanalyses were carried out by Dr. W. T. Chambers and Miss H. Rhodes. Olefinic unsaturation was determined by bromine addition (Bloomfield, *J. Soc. Chem. Ind.*, 1945, **64**, 274), and molecular weights were determined by depression of f. p. of benzene.

Squalene (14 g.) was heated with sulphur (1.4 g.) in an atmosphere of nitrogen for 3 hrs. at 140° . The product was freed from unreacted sulphur first by cooling and filtering, and finally by passage through a falling-film molecular still (Farmer and Sutton, *ibid.*, 1946, **65**, 164) at 100° . Subsequent molecular distillation of the product at 140° gave a pale yellow distillate (13 g.) having n_D^{20} 1.5031 (Found: C, 86.1; H, 12.0; S, 2.1; $\cdot\text{SH}$, 0.09; I.V., 338; M , 412. Calc. for mixture of 71% $\text{C}_{30}\text{H}_{50}\text{S}$ and 29% $\text{C}_{60}\text{H}_{100}\text{S}_6$: C, 85.7; H, 12.2; S, 2.1; I.V. 348; M , 420) which showed selective U.V. absorption at 2800 \AA. , and a reddish-brown viscous residue (1.5 g.) (Found: C, 71.15; H, 9.95; S, 18.75; $\cdot\text{SH}$, 0.3; I.V., 260 ± 15 ; M , 825. $\text{C}_{60}\text{H}_{100}\text{S}_6$ requires C, 71.1; H, 9.95; S, 18.95%; M , 1013). A 10% aqueous solution of sodium sulphite removed 9% of the sulphur contained in the residue in 3 hrs. at 100° , but was without action on the sulphur in the distillate. A sample of the residue was heated in a vacuum for 45 mins. at 160° (Found: C, 70.9; H, 9.9; S, 18.7; $\cdot\text{SH}$, 0.9%; I.V., 209). Further molecular distillation of the distillate at 110° yielded fractions respectively poorer (Found: S, 1.2%)

and richer (Found : S, 4.8%; *M*, 415) in the sulphurated component. The former of these two fractions yielded substantially pure squalene, n_D^{20} 1.4988 (Found : S, 0.4%; I.V., 360) on passage through chromatographic alumina on which the sulphurated component was strongly adsorbed.

Squalene (10 g.), sulphur (1.0 g.), zinc oxide (0.5 g.), stearic acid (0.5 g.), and mercaptobenzthiazole (0.1 g.) were heated together for 3 hrs. at 140°. Separative treatment in the molecular still yielded a distillable component (8.4 g.), n_D^{20} 1.5109 (Found : C, 83.15; H, 11.6; S, 5.3; active H, <0.01; I.V., 312; *M*, 413. Calc. for 73% $C_{30}H_{50}S$ + 27% $C_{30}H_{50}$: C, 83.1; H, 11.7; S, 5.3%; I.V., 311; *M*, 434) and a residue (1.0 g.) (Found : S, 19.95%) which was free from zinc.

This paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The author expresses his thanks to Dr. E. H. Farmer for his advice and criticism.

THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
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[Received, January 15th, 1947.]

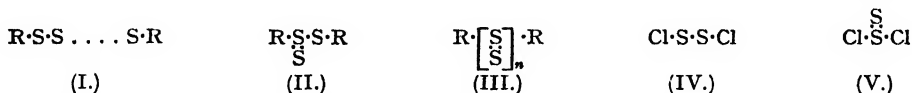
302. *The Reaction of Sulphur and Sulphur Compounds with Olefinic Substances. Part IV. The Thermal Decomposition of Organic Polysulphides, and its Contribution to the Sulphur-Olefin Reaction.*

By GEORGE F. BLOOMFIELD.

At temperatures in the region of 140° organic polysulphides undergo disproportionation resulting from thermal fission of S-S bonds and recombination of the fission products. In the presence of olefins a considerable proportion of the fission products become attached to ethylenic centres of the olefin, forming mixed mono- and poly-sulphides. The major part of the monosulphide product is fully saturated, hydrogen-capture occurring during, or subsequent to, the formation of adducts from the olefin and sulphurated fragments; unsaturation, however, appears in the polysulphide portion. The polysulphides are capable of producing monothio-cross-links between the original olefinic molecules only in so far as they are able to yield up elementary sulphur to the olefin, and when the original olefin is a polyisoprene the tendency towards the formation of a high proportion of intramolecular cyclic sulphide still further reduces the opportunity for formation of intermolecular sulphur-cross-linked products.

SINCE polysulphides are the principal products of the reaction of sulphur with olefins (Farmer and Shipley, Part I, this vol., p. 1519) an understanding of their thermal stability and of their further reaction with olefins is clearly of importance in clarifying the general problem of chemical changes associated with the olefin-sulphur reaction and the related problem of rubber vulcanisation.

The structure of polysulphides has long presented difficulty in respect of the necessity for deciding between their representation by the wholly linear structures (I) or by co-ordinated structures of type (II) or (III). Based principally on evidence provided by X-ray data (Katz,



Trans. Faraday Soc., 1936, **32**, 77) and by the lability of a considerable proportion of the sulphur atoms on treatment with alkali (Patrick, *ibid.*, p. 347) or with sodium sulphite (Parker, *India Rubber J.*, 1945, **108**, 387), a co-ordinated structure has been generally assigned to those polysulphides obtained by the interaction of organic halides and alkali polysulphides. Evidence based on the lability of sulphur atoms is, however, no certain criterion of the presence of co-ordinated sulphur atoms, since it is now shown that a comparable lability is exhibited by two of the four sulphur atoms in tetrasulphides obtained by the interaction of thiols and sulphur monochloride. Whether one accepts a linear (IV) or branched (V) structure for sulphur monochloride, it follows that three of the four sulphur atoms of the derived tetrasulphide must be in a linear chain, so that when two sulphur atoms are removed, at least one of them must have been abstracted from a linear chain. The electron-diffraction investigations of Palmer (*J. Amer. Chem. Soc.*, 1938, **60**, 2360) indicate the linear structure (IV) for the monochloride, and since, moreover, a recent ultra-violet absorption study by Koch (in the press) provides convincing evidence of a linear structure of some of the organic polysulphides which form the basis of the present work, it seems fully justifiable to assume linear structures both for the tetrasulphides prepared by the interaction of thiols with sulphur monochloride and for the polysulphide products of the sulphur-olefin reaction. The chemical behaviour of these poly-

sulphides is not at variance with the assumption of a linear structure, nor is a linear structure inconsistent with the ring formulation of the polymeric organic polysulphides (Fuller, *Chem. Reviews*, 1940, **26**, 160).

The precise mechanism of the removal of sulphur from polysulphides by sodium sulphite or sodium hydroxide is not altogether clear, although when the former reagent is used it appears certain that the polysulphide is converted mainly into disulphide (Armstrong, Little, and Doak, *Ind. Eng. Chem.*, 1944, **36**, 628) although a small proportion (not exceeding 10%) of it undergoes reduction to thiols. Probably there is fission of the sulphur chain, giving thio-radicals which recombine to form disulphides, or, to a small extent, are reduced to thiols, while the sulphur liberated converts sodium sulphite into thiosulphate.

Although the thermal decomposition at 170–180° of some polysulphides containing olefinic unsaturation gives thiols and hydrogen sulphide, together with a sulphurated product of much reduced hydrogen content (Farmer and Shipley, Part I), it is now found that the thermal decomposition of a saturated tetrasulphide at somewhat lower temperatures (140–150°) gives only disproportionation products (lower and higher polysulphides), neither thiol nor hydrogen sulphide being formed. Moreover, at temperatures below 120°, the tetrasulphides could generally be distilled unchanged.

Interaction of a polysulphide $R \cdot S_x \cdot R$ with cyclohexene in the temperature range 140–180° gave sulphurated products of the type $R \cdot S_y \cdot R'$ ($y < x$) in which R was an organic group from the original polysulphide and R' was cyclohexyl or cyclohexenyl, together with disulphides R_2S_2 derived from the original polysulphide, and cyclohexyl cyclohexenyl di- and poly-sulphides. The latter were similar to the polysulphides resulting from the reaction of sulphur itself with cyclohexene, but contained a smaller sulphur chain. Diethyl tetrasulphide and cyclohexene yielded rather complex mixtures in which the more volatile components could not be adequately separated by distillation, so it was not possible to confirm or to exclude the presence of either the cyclohexanethiol or the cyclohexene episulphide expected from the work of Jones and Reid (*J. Amer. Chem. Soc.*, 1938, **60**, 2452). The presence of some cyclohexyl ethyl sulphide was, however, established beyond doubt by the isolation of cyclohexyl ethyl sulphone on oxidation of the most volatile portion of the reaction product. When polysulphides containing larger organic groups were used, the separation of volatile components was facilitated, although the separation of non-volatile components became correspondingly more difficult. In spite of the most careful search, cyclohexene episulphide could in no case be detected, and the total amount of cyclohexanethiol formed, together with thiols derived from the original polysulphide, was extremely small. The most volatile products in every instance consisted of mixed mono-sulphides of the type $C_6H_{11}S \cdot R$, R being an organic group of the original tetrasulphide, although when di-*p*-chlorophenyl tetrasulphide reacted with cyclohexene some dicyclohexyl sulphide was formed in addition to *p*-chlorophenyl cyclohexyl sulphide. The origin of the dicyclohexyl sulphide in the latter case is obscure.

Unsaturated polysulphides obtained by reaction of sulphur with cyclohexene reacted at 140° with further cyclohexene to give polysulphides with shorter sulphur chains, separable into components none of which appeared to be of greater sulphur chain-length than a tetrasulphide, with an increasing tendency towards saturation in the more volatile components. The amount of material available did not, however, permit of the isolation of a monosulphide.

It is accordingly suggested that the thermal decomposition of polysulphides at temperatures below 180° involves thermal fission of $-S-S-$ bonds. In the absence of a second reactive substance, recombination of fission products regenerates the polysulphides or gives disproportionation products by union of dissimilar fission products. In the presence of an olefin the fission products (or the thiols derived therefrom by hydrogen capture) may either add to the ethylenic linkage, forming, ultimately, a saturated sulphide, or the fission product may link with an allylic radical to form an unsaturated mono-, di-, or poly-sulphide. Simultaneously, reaction occurs between the olefin and sulphur liberated from the sulphur chain of the polysulphide, and since the sulphur may be presumed to be liberated in a rather reactive (possibly atomic) form, the length of the sulphur chain in these products is not large.

It follows that in the reaction of sulphur with olefins, secondary products resulting from the reaction of primarily-formed polysulphides with the olefins are to be expected, especially when the olefin is present in considerable excess. When polysulphides reacted with dihydromyrcene, a considerable quantity of dihydromyrcene cyclic sulphide, identical with that obtained from dihydromyrcene and sulphur (Farmer and Shipley, Part I), was formed. Of particular interest from the point of view of the general reaction of sulphur with polyisoprenes is the ready formation of the cyclic sulphide when dihydromyrcene polysulphide itself was heated with dihydro-

myrcene, and it is hoped soon to ascertain whether the cyclic sulphide formed in the reaction of polyisoprenes with sulphur is a primary product of the olefin-sulphur reaction, or a secondary product formed solely by interaction of polyisoprene polysulphides with the excess of hydrocarbon usually present in these reactions.

Since it is now generally accepted that rubber vulcanisation requires the presence of intermolecular cross-linkages, the combination with rubber of sulphurated fragments of polysulphides alone should not cause vulcanisation unless the sulphurated fragments are themselves polyfunctional (cf. Patrick, U.S.P. 2,235,621). Dialkyl tetrasulphides react fairly readily with rubber, giving *soluble* products containing 2 or 3 units % of combined sulphur which is undoubtedly contained in sulphurated polysulphide fragments added at ethylenic centres of the rubber, since it is well established that products of the reaction of sulphur with rubber, containing considerably less combined sulphur, are quite insoluble. Both the H:C ratio and loss of unsaturation in these tetrasulphide-rubber reaction products are consistent with the postulated incorporation of sulphurated fission products with the rubber; moreover, the product of interaction of di-*p*-chlorophenyl tetrasulphide with rubber contains chemically-combined chlorine as well as sulphur. The insolubility of the latter product is attributed to the presence of sulphur in excess of that resulting from simple addition of sulphurated polysulphide fragments, and it appears certain that some degree of cross-linking has been brought about by the reaction of sulphur itself, liberated from the sulphur chain of the polysulphide. These ideas are consistent with Throdahl and Beavers's observation (*Rubber Chem. Tech.*, 1945, **18**, 110) that, although dialkyl tetrasulphides are incapable of vulcanising rubber, yet some degree of vulcanisation is observed with certain aromatic polysulphides.

It is known that in dehydrogenation reactions at elevated temperatures disulphides are as effective as sulphur itself, the disulphide linkage undergoing cleavage (Ritter and Sharpe, *J. Amer. Chem. Soc.*, 1937, **59**, 2351). If thermal dissociation of disulphides into RS· radicals (cf. Schönberg, *Ber.*, 1933, **66**, 1932) is appreciable at 140°, then it might be expected that disulphides in the presence of sulphur and an olefin would react essentially as polysulphides, and, furthermore, disulphides themselves might be expected to enter into reaction with olefins. Only scanty evidence of the latter type of reactivity has been obtained with disulphides at temperatures below 180°, and diphenyl disulphide, which might be expected to dissociate rather more readily than dialkyl disulphides, proved to be entirely without action on cyclohexene at 180°. Farmer and Shipley have, however, observed the formation of considerable amounts of mercaptobenzthiazole on heating together benzthiazole disulphide and cyclohexene at 140°. Diethyl disulphide and sulphur, heated together at 140–150°, gave no more than trace amounts of polysulphide, and when there was also an olefinic substance present reaction occurred exclusively between the sulphur and the olefin, giving the usual polysulphide products, without any indication of participation of the dialkyl disulphide.

EXPERIMENTAL.

Microanalyses were carried out by Dr. W. T. Chambers, Miss E. Farquhar, and Miss H. Rhodes. Olefinic unsaturation was determined by bromine addition (Bloomfield, *J. Soc. Chem. Ind.*, 1945, **64**, 274).

All the experiments with polysulphides were conducted in sealed glass tubes or glass flasks.

Preparation of Tetrasulphides.—Tetrasulphides were prepared by a modification of the method described by Bezzi (*Gazzetta*, 1935, **65**, 693). A 10% solution of sulphur monochloride (1 mol.) in carbon disulphide was added at room temperature to a 10% solution of the appropriate thiol (2.1 mols.) in the same solvent, and as soon as the initial brisk evolution of hydrogen chloride had subsided the solution was gently boiled for 30 minutes under a reflux condenser. The solvent was then removed at room temperature under reduced pressure, and, with the exception of di-*p*-chlorophenyltetrasulphide, which crystallised from the residue, the residual tetrasulphide was finally distilled.

Properties of Tetrasulphides.—Diethyl (sample A) had b. p. 58–60°/0.1 mm., n_D^{20} 1.6172; di-*n*-butyl was molecularly distilled at 56° in a falling-film molecular still (Farmer and Sutton, *J. Soc. Chem. Ind.*, 1946, **65**, 164) and had n_D^{20} 1.5772; diisooamyl, molecularly distilled at 56°, had n_D^{20} 1.5542; dicyclohexyl, molecularly distilled at 100°, had n_D^{20} 1.6050 (Found: C, 49.0; H, 7.45; S, 43.3. $C_{12}H_{22}S_4$ requires C, 48.95; H, 7.55; S, 43.5%); diphenyl, molecularly distilled at 110°, had n_D^{20} >1.7; di-*p*-chlorophenyl, recrystallised from light petroleum, had m. p. 57° (Found: C, 40.65; H, 2.35; Cl, 20.3; S, 36.25. $C_{12}H_8Cl_2S_4$ requires C, 41.05; H, 2.30; Cl, 20.2; S, 36.5). The author is also indebted to Dr. F. W. Shipley for a sample (B) of diethyl tetrasulphide, b. p. 45°/0.01 mm., n_D^{20} 1.610, prepared by interaction of ethyl iodide and sodium tetrasulphide. The proportion of the total sulphur content (hereinafter designated "removable sulphur") removable by a boiling 10% aqueous solution of sodium sulphite was determined for each of these tetrasulphides (Table I).

Thermal Decomposition of Dicyclohexyl Tetrasulphide.—The tetrasulphide (17.1 g.) in purified cyclohexane (50 c.c.) was heated for 4 hrs. at 140°, air being excluded. Molecular distillation of the solvent-free product yielded a relatively small amount (2.9 g.) of material of reduced sulphur content which had n_D^{20} 1.5816 (Found: C, 53.7; H, 8.35; S, 38.0; removable S, 3 hrs., 25.2, 8 hrs., 31.8%), a considerable amount (9.6 g.) of mainly unchanged dicyclohexyl tetrasulphide, n_D^{20} 1.6032 (Found: C, 49.75;

TABLE I.

Tetrasulphide.	Removable sulphur, % :	
	3 hrs. at 100°.	8 hrs. at 100°.
Diethyl (A).....	50	50
Diethyl (B).....	49	not determined
Di- <i>n</i> -butyl.....	30	45
Diisoamyl.....	44	50
Dicyclohexyl.....	11	44
Diphenyl.....	50	52
Di- <i>p</i> -chlorophenyl.....	50	50

H, 7.55; S, 42.3; removable S, 3 hrs., 9.2; 8 hrs., 37.2%, and a relatively small amount (1.7 g.) of viscous *dicyclohexyl hexasulphide*, n_D^{20} 1.664 (Found: C, 39.8; H, 6.15; S, 53.7; removable S, 3 hrs., 43.2, 8 hrs., 49.2. $C_{12}H_{22}S_6$ requires C, 40.2; H, 6.2; S, 53.6%). The infra-red spectrum of the hexasulphide revealed no unsaturation.

Reaction of Tetrasulphides with Olefins.—(1) *Diethyl tetrasulphide and cyclohexene*. The tetrasulphide (sample A, 20 g.) and cyclohexene (50 c.c.) were heated together for 4 hrs. at 140° in the absence of air. After removal of unchanged cyclohexene (34 g.), the product was separated into a wide range of fractions, b. p. 35–75°/0.1 mm. (total weight 18 g.), leaving a viscous residue (6 g.), care being taken to avoid heating above 130° during the distillation. The recovered cyclohexene contained a trace of ethanethiol, but no carbon disulphide could be detected. Redistillation of the volatile portion of the reaction product gave the following main fractions: (i) b. p. 75–77°/13 mm. (3.5 g.), n_D^{17} 1.5304 (Found: C, 46.05; H, 8.55; S, 46.0; removable S, 2 hrs., 25.9%); (ii), b. p. 77–79°/13 mm. (2.4 g.), n_D^{17} 1.5388 (Found: C, 42.35; H, 8.05; S, 48.95; removable S, 2 hrs., 28.8%); (iii) b. p. 79°/13 mm. (1.4 g.), n_D^{17} 1.5490 (Found: C, 38.4; H, 8.25; S, 53.4; removable S, 2 hrs., 30.5%), and (iv) b. p. 55–75°/0.1 mm. (8.4 g.), n_D^{17} 1.5970 (Found: C, 34.7; H, 6.4; S, 59.3; removable S, 2 hrs., 47.3%). Further fractionation of fraction (iv) gave sub-fractions of unchanged *n*. Since the H : C ratio of fractions (i), (ii), and (iv) indicated the presence of a considerable proportion of cyclohexyl groups, the most volatile fraction (i) was reduced by sodium in alcohol, whereby di- and poly-sulphides were converted into sodium mercaptides. Oxidation with acid permanganate of the alkali-insoluble components of the reduced product gave cyclohexyl ethyl sulphone, m. p. 34° (Found: C, 54.55; H, 9.30; S, 18.1. $C_8H_{16}O_2S$ requires C, 54.55; H, 9.15; S, 18.2%). The non-volatile portion of the original reaction product contained mainly cyclohexyl and cyclohexenyl groups (Found: C, 38.6; H, 5.7; S, 54.5; removable S, 4 hrs., 51%). Only a trace of cyclohexanethiol was detected in the reaction product, and no cyclohexene episulphide was isolated.

(2) *Diisoamyl tetrasulphide and cyclohexene*. The tetrasulphide (17 g.) and cyclohexene (50 c.c.) were heated together for 4 hrs. at 180° in the absence of air. Distillation of the reaction product yielded (a) unchanged cyclohexene (25 c.c.), (b) a fraction, b. p. 60–75°/0.01 mm. (21.2 g.), and (c) a residue (15.7 g.) not distillable below 100°/0.01 mm. The unchanged cyclohexene was carefully redistilled (Fenske column) and the residue was united with traces of liquid of b. p. <60°/0.01 mm. isolated during the preliminary separation; the combined liquids (0.5 g.), redistilled at 13 mm., consisted entirely of thiols (Found: C, 64.8; H, 10.4; S, 24.8; active H, 0.75% = 24.0% S as $-SH$). Fraction (b) was redistilled at 0.1 mm., and yielded mainly cyclohexyl isoamyl sulphide (12.5 g.), b. p. 58–60°, n_D^{20} 1.4860 (Found: C, 70.2; H, 11.6; S, 18.2; removable S, nil. Calc. for $C_{11}H_{22}S$: C, 71.0; H, 12.0; S, 17.2%), together with the following fractions of higher sulphur content: (i) b. p. 60–62° (2.7 g.), n_D^{20} 1.4909 (Found: C, 69.75; H, 11.45; S, 18.75%); (ii) b. p. 62–65° (0.6 g.), n_D^{20} 1.6018; (iii) b. p. 65–70° (2 g.), n_D^{20} 1.5142 (Found: C, 68.55; H, 10.7; S, 20.5%); and (iv) b. p. 70–75° (2.2 g.), n_D^{20} 1.5218 (Found: C, 65.25; H, 10.2; S, 24.4; removable S, 3 hrs., 12%; *M*, 198; *I. V.*, 46). Permanganate oxidation of the bulk fraction of cyclohexyl isoamyl sulphide gave the sulphone (yield, 60%), m. p. 57–58° (Found: C, 60.25; H, 10.2; S, 14.7%. Calc. for $C_{11}H_{22}SO_2$: C, 60.5; H, 10.2; S, 14.65%), which had mixed m. p. 57° with an authentic specimen of m. p. 57° (Cunneen, this vol., p. 36). The non-distillable residue (c) was passed through the molecular still at 56°, at which temperature about half of the material was volatile. The distillate (6.3 g.), a pale yellow mobile oil, had n_D^{20} 1.5458, and consisted mainly of disulphides (Found: C, 63.8; H, 9.55; S, 26.85; removable S, 8 hrs., 1.5%; *M*, 215). The brown, rather viscous residue (6.1 g.), n_D^{20} 1.5818, was of greater molecular complexity (Found: C, 61.35; H, 8.4; S, 30.0; removable S, 8 hrs., 10.7%; *M*, 318). Infra-red examination of both distillate and residue showed the presence of isoamyl groups, and also revealed the presence of unsaturation of an apparently conjugated type.

A similar experiment conducted at 140° with 12.7 g. of the tetrasulphide gave no cyclohexene episulphide and no more than a trace of thiols. Some cyclohexyl isoamyl sulphide (2.9 g.) was isolated from the crude reaction product; on passing the remainder through the molecular still the volatile portion (7.4 g.), containing considerable unchanged diisoamyl tetrasulphide, had n_D^{20} 1.5481 (Found: C, 48.05; H, 8.55; S, 43.1; removable S, 3 hrs., 37.0; 8 hrs., 43.5%; *M*, 250), but the non-volatile residue (2.1 g.) had n_D^{20} 1.5958 and probably consisted mainly of cyclohexyl isoamyl polysulphide and cyclohexenyl isoamyl polysulphide (Found: C, 43.35; H, 7.0; S, 48.3; removable S, 3 hrs., 45.2; 8 hrs., 53.0%; *M*, 312. Calc. for $C_6H_{11}S_{2.5}C_6H_{10.5}$: *M*, 301). The high proportion of removable sulphur after 3 hrs. at 100° indicates the absence of any appreciable amount of dicyclohexyl tetrasulphide. Treatment of the non-volatile residue with further cyclohexene for 3 hrs. at 140° gave an increase in weight of 23%, and pot-still molecular distillation of the product gave two fractions of substantially lower sulphur content than the original material; the distillate had n_D^{20} 1.5358 (Found: C, 56.7; H, 9.3; S, 33.85; removable S, 3 hrs., 28.7; 8 hrs., 30.7%, corresponding to $C_6H_{11}S_{2.5}C_6H_{10.5}$) and the residue had n_D^{20} 1.6062 (Found: C, 48.95; H, 7.4; S, 42.8; removable S, 3 hrs., 29.7; 8 hrs., 39.2%, corresponding to $C_6H_{11}S_{3.5}C_6H_{10.5}$).

(3) *Dicyclohexyl tetrasulphide and cyclohexene*. 9.2 G. of the tetrasulphide, heated for 3 hrs. at

180° with excess of cyclohexene, gave 9 g. of dicyclohexyl sulphide free from unsaturation (Found: C, 72.7; H, 11.2; S, 16.2. Calc. for $C_{12}H_{22}S$: C, 72.7; H, 11.15; S, 16.15%), together with higher sulphides containing unsaturation, e.g., a disulphide (5.8 g.), b. p. >100°/0.01 mm., n_D^{20} 1.5792 (Found: C, 61.6; H, 8.75; S, 29.3%). Oxidation of the dicyclohexyl sulphide gave dicyclohexyl sulphone, m. p. 132.5°, in 80% yield (Found: C, 62.4; H, 9.7; S, 13.65. Calc. for $C_{12}H_{22}O_2S$: C, 62.55; H, 9.65; S, 13.9%).

(4) *Di-p-chlorophenyl tetrasulphide and cyclohexene.* The product obtained by heating together the tetrasulphide (23.6 g.) and cyclohexene (50 c.c.) was separated by one passage through the molecular still at 56° into a pale yellow distillate (A, 14.8 g.) and a golden brown residue (B, 25 g.) which on a second passage through the still at 80° was further separated into a pale yellow distillate (C, 16.0 g.) and a residue (D, 7.3 g.). The distillate A, which had n_D^{20} 1.5661 (Found: C, 65.9; H, 7.8; Cl, 11.25; S, 15.05%), was redistilled from a flask at 0.001 mm., giving the following fractions: (i) b. p. 72–80° (0.8 g.), n_D^{20} 1.5252; (ii) b. p. 80–85° (2.0 g.), n_D^{20} 1.5342 (Found: C, 70.75; H, 9.95; Cl, 3.9; S, 15.3. Calc. for 24.6% $C_{12}H_{18}ClS$ + 73.4% $C_{12}H_{22}S$: C, 69.0; H, 9.80; Cl, 3.9; S, 15.3%), (iii) b. p. 85–92° (2.7 g.), n_D^{20} 1.5541 (Found: C, 68.45; H, 8.7; Cl, 7.9; S, 15.05. Calc. for 50.5% $C_{12}H_{18}ClS$ + 49.5% $C_{12}H_{22}S$: C, 68.05; H, 8.9; Cl, 7.9; S, 15.1%), (iv) b. p. 92–96° (4.1 g.), n_D^{20} 1.5762 (Found: C, 65.3; H, 7.05; Cl, 13.95; S, 14.4. Calc. for 89.2% $C_{12}H_{18}ClS$ + 10.8% $C_{12}H_{22}S$: C, 64.5; H, 7.1; Cl, 13.95; S, 14.3%), and a liquid residue (v), not distillable without overheating, n_D^{20} 1.5808, from which crystallised *p-chlorophenyl cyclohexyl sulphide*, m. p. 25° (Found: C, 63.85; H, 6.8; Cl, 15.75; S, 14.05. $C_{12}H_{18}ClS$ requires C, 63.55; H, 6.7; Cl, 15.65; S, 14.1%). Oxidation of fraction (iv) gave a 62% yield of *p-chlorophenyl cyclohexyl sulphone*, m. p. 68–69° (Found: C, 55.9; H, 5.85; Cl, 13.95; S, 12.4. $C_{12}H_{18}O_2ClS$ requires C, 55.7; H, 5.85; Cl, 13.7; S, 12.4%).

(5) *cycloHexyl cyclohexenyl polysulphide and cyclohexene.* A typical polysulphide (Found: C, 34.55; H, 4.85; S, 59.6%), obtained by the action of sulphur on cyclohexene, was heated with an excess of cyclohexene for 3 hrs. at 140°. There was a weight increase of 14% and the product yielded a distillate (pot still) which had n_D^{20} 1.5805 (Found: C, 56.1; H, 8.1; S, 36.15; removable S, 8 hrs., 33.2%) and a residue which had n_D^{20} 1.6260 (Found: C, 51.0; H, 7.0; S, 40.9; removable S, 8 hrs., 29.6%).

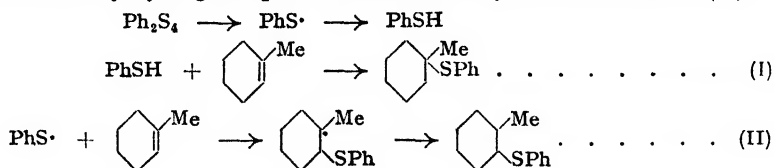
(6) *Diphenyl tetrasulphide and dihydromyrcene.* The tetrasulphide (19.1 g.) and dihydromyrcene (50 c.c.), heated together for 3 hrs. at 150° in the absence of air, yielded dihydromyrcene cyclic sulphide (3.8 g.) and a reddish-brown oil (29.7 g.) which was separated by passage through the molecular still at 80° into a volatile red liquid (21.7 g.) (Found: C, 72.4; H, 7.9; S, 18.7%) which deposited considerable diphenyl disulphide, and a brown viscous residue (4.0 g.) (Found: C, 61.85; H, 7.45; S, 31.7%).

(7) *Dihydromyrcene polysulphide and dihydromyrcene.* The polysulphide (5.5 g.), obtained by the action of sulphur on dihydromyrcene, and freed from cyclic sulphide and free sulphur by repeated passage through the molecular still, was heated with dihydromyrcene (20 c.c.) for 3 hrs. at 145° and yielded 3.3 g. of dihydromyrcene cyclic sulphide together with 6.5 g. of non-volatile matter (Found: C, 57.35; H, 8.6; S, 33.35%).

(8) *Tetrasulphides and rubber.* The tetrasulphides were incorporated into the rubber by milling, the mixtures were heated in sealed evacuated tubes for 3 hrs. at 140°, and the products were extracted with acetone and with chloroform if they were sufficiently insoluble. Diethyl tetrasulphide (0.76 g.) and rubber (5 g.) yielded a reddish-brown product (Found: C, 84.8; H, 11.65; S, 2.8%; I.V., 328) which was soluble in benzene and in chloroform. Di-*p-chlorophenyl tetrasulphide* (1.1 g.) and rubber (4 g.) yielded an insoluble product (Found: C, 79.1; H, 10.45; Cl, 2.65; S, 7.25%).

This paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The author expresses his thanks to Dr. E. H. Farmer for his advice and criticism, and to Mr. N. Sheppard for infra-red examination of some of the polysulphides.

Note added in Proof.—Since the above papers were submitted the reaction mechanism involved in the formation of saturated monosulphides by the interaction of polysulphides with olefins has been clarified by a study of the reaction of diphenyl tetrasulphide with 1-methylcyclohexene. Since the major reaction product is phenyl 1-methylcyclohexyl sulphide and not phenyl 2-methylcyclohexyl sulphide it appears certain that the reaction involves hydrogen-capture by the fission product of the polysulphide and addition of the resulting thiol to the double bond by a polar mechanism (I) rather than by a radical addition of the fission product to the double bond followed by hydrogen-capture at the other ethylenic carbon atom (II).



The structure of the sulphide formed was confirmed by mixed m. p. (76°) of the corresponding sulphone with the phenyl 1-methylcyclohexyl sulphone of m. p. 76° described by Cunneen (*loc. cit.*).

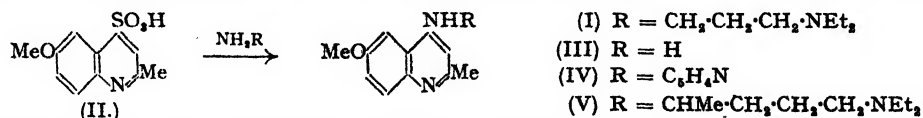
303. Derivatives of 6-Methoxyquinaldine with Basic Substituents in the 4-Position.

By JAMES WALKER.

Attention is directed to the smooth replacement of the sulphonic acid group in quinoline-4-sulphonic acids by reaction with amines as a means of preparing quinolines substituted in the 4-position by basic groups.

IN contrast with the activity shown by certain 4-dialkylaminoalkylamino-6-methoxyquinolines in bird malaria (Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, 7, 1896), no activity was observed in analogous quinaldines (e.g., Kermack and Smith, *J.*, 1931, 3096; Krichevskii *et al.*, *J. Microbiol. Epidemiol. Immunobiol. Russia*, 1935, 14, 642). In view of the greater accessibility of the quinaldines as compared with the quinolines of this type, the present author, towards the end of 1941, began a further investigation of other 6-methoxyquinaldines, but, while the work was still in progress, essentially the same project was independently covered by Holcomb and Hamilton (*J. Amer. Chem. Soc.*, 1942, 64, 1309), who actually record the observation of antimalarial activity in 4- γ -diethylaminopropylamino-6-methoxyquinaldine (I), and the writer's interest was then withdrawn from this topic although the work, as now described below, differed in technical detail from that of Holcomb and Hamilton. In the interval, however, much attention has been devoted to the subject of quinolines substituted in the 4-position by basic side-chains in view of the marked antimalarial properties of resochin (7-chloro-4- δ -diethylamino- α -methylbutylaminoquinoline), which can be regarded as being derived from mepacrine by ablation of the methoxylated benzene ring, and the corresponding 3-methyl compound, sontochin (D.R.-P. 683,692; U.S.P. 2,233,970). Much has recently been published in the United States in this connection (e.g., Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, 68, 1208, 1214; Tarbell *et al.*, *ibid.*, p. 1217; Carmack *et al.*, *ibid.*, p. 1220; Pearson, Jones, and Cope, *ibid.*, p. 1225; Riegel *et al.*, *ibid.*, p. 1229; Breslow *et al.*, *ibid.*, p. 1232; Elderfield *et al.*, *ibid.*, p. 1250). The method regularly used for the introduction of the aliphatic basic side-chains into the 4-position of quinolines has been to condense the appropriate 4-chloro-compounds with the appropriate amines at a high temperature, and fair yields have been reported as a rule. Occasionally, phenol has been added as a catalyst but it does not appear to have the same marked influence in the quinoline series as it has with 5-chloroacridines (cf. Magidson and Grigorowsky, *Ber.*, 1936, 69, 400). Potassium iodide has also been applied as a catalyst but there is little evidence of its efficaciousness, and glacial acetic acid has been used as a solvent in such condensations with aliphatic amines (Meyer and Drutel, *Compt. rend.*, 1936, 205, 148) although its use is more familiar with anilines (e.g., Fischer, Diepolder, and Wölfel, *J. pr. Chem.*, 1925, 109, 59).

The present paper records the use of 6-methoxyquinaldine-4-sulphonic acid (II) for this purpose in an application of a method outlined in the patent literature (D.R.-P. 615,184). In the original patent, quinoline-2- or -4-sulphonic acids were condensed with amines with or without the addition of a catalyst, such as zinc chloride, but the latter was used in the experiments described below, in which (II) has been condensed with ammonia to give 4-amino-6-methoxyquinaldine (III), with α -aminopyridine to give 4- α -pyridylamino-6-methoxyquinaldine (IV) in poor yield, with γ -diethylaminopropylamine to give (I) (characterised as the dihydrochloride), and with δ -diethylamino- α -methylbutylamine to give 4- δ -diethylamino- α -methylbutylamino-6-methoxyquinaldine (V) (characterised as the dihydrobromide). The sulphonic



acid (II) was obtained in practically quantitative yield from 4-chloro-6-methoxyquinaldine and sodium sulphite in aqueous solution (cf. Besthorn and Geisselbrecht, *Ber.*, 1920, 53, 1017), and subsequent condensation with amines proceeded as a smooth homogeneous reaction affording products which readily crystallised in the crude state (cf. Bachman and Cooper, *J. Org. Chem.*, 1944, 9, 307). Holcomb and Hamilton (*loc. cit.*) failed to isolate a satisfactory condensation product from 4-chloro-6-methoxyquinaldine and α -aminopyridine, but a small yield of the expected product was readily isolated using the sulphonic acid. Furthermore, condensation with ammonia proceeded particularly readily with the sulphonic acid in marked contrast with

the behaviour of 4-chloroquinolines (cf. Elderfield *et al.*, *loc. cit.*; Backeberg and Marais, *J.*, 1942, 381).

Tests for therapeutic activity in *P. relictum* infections in canaries were kindly carried out by Dr. Ann Bishop at the Molteno Institute, Cambridge, on sodium 6-methoxyquinaldine-4-sulphonate, 4- α -pyridylamino-6-methoxyquinaldine (IV), and 4- δ -diethylamino- α -methylbutylamino-6-methoxyquinaldine (V) dihydrobromide, but no activity was detected. It is now obvious that a methyl group in the 2-position in quinolines, though not in the 3-position (cf. sontochin), has a marked dystherapeutic effect probably by presenting to the host a point of metabolic attack.

EXPERIMENTAL.

6-Methoxyquinaldine-4-sulphonic Acid (II).—Ethyl β -*p*-anisidinocrotonate (Coffey, Thomson, and Wilson, *J.*, 1936, 856) was cyclised by Limpach's technique (*Ber.*, 1931, 64, 969) and the resulting 4-hydroxy-6-methoxyquinaldine was converted into the chloro-compound in 90% yield following the method of Fischer *et al.* (*loc. cit.*). 4-Chloro-6-methoxyquinaldine (5 g.) was refluxed with an aqueous solution (40 c.c., adjusted to pH 8 with *N*-hydrochloric acid) of sodium sulphite heptahydrate (12 g.) until a homogeneous solution was obtained (3½ hours) and then for a further ¼ hour. The solution, treated with norite, was filtered and cooled, affording a copious separation of colourless prisms of the sodium salt. The free acid, precipitated by acidifying an aqueous solution of the sodium salt to Congo-red with 16% hydrochloric acid, separated from water in pale cream-coloured hydrated prisms which lost part of the water of crystallisation in a vacuum desiccator, darkened at about 296°, and had m. p. 302–303° (decomp.) (Found: C, 48.6; H, 5.0; N, 5.2. $C_{11}H_{11}O_4NS \cdot H_2O$ requires C, 48.7; H, 4.8; N, 5.2%). The yield was nearly quantitative.

4-Amino-6-methoxyquinaldine (III).—6-Methoxyquinaldine-4-sulphonic acid (6 g.), 25% aqueous ammonia solution (30 c.c.), and zinc chloride (1 g.) were heated in a sealed tube at 130° for 20 hours. On cooling, large yellow plates were deposited. The mixture was warmed to effect solution, cooled, and treated with excess of 2*N*-sodium hydroxide (25–30 c.c.). The precipitated oil rapidly crystallised in colourless needles (3.75 g.; 84%), m. p. 206°. Recrystallisation from dilute aqueous alcohol afforded thin plates, m. p. 208–209° (Found: C, 70.0; H, 6.5; N, 14.9. Calc. for $C_{11}H_{12}ON_2$: C, 70.2; H, 6.4; N, 14.9%). Koenigs and v. Loesch (*J. pr. Chem.*, 1935, 143, 59) record m. p. 211–213°, and Backeberg and Marais (*loc. cit.*) record m. p. 209°.

4- α -Pyridylamino-6-methoxyquinaldine (IV).—6-Methoxyquinaldine-4-sulphonic acid (5.06 g.), freshly distilled α -aminopyridine (3.8 g.), zinc chloride (1 g.), and water (25 c.c.) were heated in a sealed tube at 140° for 30 hours. The product was distributed between ether and excess of 2*N*-sodium hydroxide. The ether was well washed with water, dried, and evaporated, affording a cream-coloured solid (0.33 g.; 6.2%), which separated from benzene in rosettes of fine colourless prisms, m. p. 196–197° (Found: C, 72.6; H, 5.7; N, 15.5. $C_{16}H_{14}ON_2$ requires C, 72.5; H, 5.7; N, 15.8%).

4- γ -Diethylaminopropylamino-6-methoxyquinaldine (I) Dihydrochloride.—6-Methoxyquinaldine-4-sulphonic acid (5.06 g.), γ -diethylaminopropylamine (4.3 g.), zinc chloride (1.2 g.), and water (18 c.c.) were heated in a sealed tube at 140° for 24 hours. The product was distributed between ether and 3*N*-sodium hydroxide. The ethereal solution was well washed with water, dried, and evaporated, affording a stiff pale yellow syrup which crystallised completely in the form of transparent plates (4.26 g.; 71%); the solid did not remelt on the boiling water-bath. The base was dissolved in a small volume of warm alcohol and treated with the calculated volume of alcoholic hydrochloric acid. The dihydrochloride, obtained on evaporation, separated from ethyl alcohol–ethyl acetate (1 : <1) in minute clusters of colourless prisms, m. p. 134° (Found, in material dried over sulphuric acid in a vacuum: C, 53.7, 54.2; H, 7.9, 7.8; N, 10.5. $C_{18}H_{27}ON_3 \cdot 2HCl \cdot 1½H_2O$ requires C, 53.9; H, 8.0; N, 10.5. Calc. for $C_{18}H_{27}ON_3 \cdot 2HCl \cdot 2H_2O$: C, 52.7; H, 8.0; N, 10.2%). Holcomb and Hamilton (*loc. cit.*) obtained a dihydrate, and record m. p. 126–127°; Van Arendonk and Shonle (*J. Amer. Chem. Soc.*, 1944, 66, 1284) record m. p. 125–126°.

4- δ -Diethylamino- α -methylbutylamino-6-methoxyquinaldine (V) Dihydrobromide.—6-Methoxyquinaldine-4-sulphonic acid (7.6 g.), δ -diethylamino- α -methylbutylamine (9.6 g.), zinc chloride (1 g.), and water (20 c.c.) were heated in a sealed tube at 150° for 20 hours. The product was isolated as in the preceding case and the base, obtained initially as an amber syrup (6.6 g.; 67%), rapidly crystallised, affording a cream-coloured solid, m. p. 120–122°, clearing at 123° (Found: OMe, 9.5. $C_{26}H_{33}ON_2$ requires OMe, 9.4%). The dihydrobromide, obtained by neutralisation with the calculated volume of *N*-hydrobromic acid and evaporation to dryness, separated from ethyl alcohol–ethyl acetate (approx. 1 : 2) in clusters of colourless radiating prisms, m. p. 197–198° (Found: C, 48.7; H, 6.7; N, 8.4; Br, 32.3. $C_{26}H_{33}ON_2 \cdot 2HBr$ requires C, 48.9; H, 6.7; N, 8.6; Br, 32.6%). The dihydrochloride of this base has been described by Holcomb and Hamilton (*loc. cit.*).

The author is greatly indebted to Dr. Ann Bishop for carrying out the antimalarial tests and to Mr. L. V. Sharp for assistance in the preparation of starting materials.

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[Received, January 17th, 1947.]

304. *Strychnine and Brucine. Part XLVII. Oxodihydroneostrychnine and Oxodihydromethoxymethyl dihydroneostrychnine.*

By R. N. CHAKRAVARTI, K. H. PAUSACKER, and SIR ROBERT ROBINSON.

It is shown that bases of the *neo*-series are characterised by facile oxidation to oxo-derivatives formed by addition of one atom of oxygen. The carbon-nitrogen skeleton of strychnine is found unaltered in reduction products of these substances.

In the course of attempts to prepare the methiodide of methoxymethyl dihydroneostrychnidine in methanolic solution it was found that oxidation occurred and the product was termed oxymethoxymethyl dihydroneostrychnidine-A, m. p. 235°. It was convertible into an isomeride-B, m. p. 280° (285°), in various ways, for example by boiling with xylene or acetone (Clemo, Perkin, and Robinson, J., 1927, 1608). No semicarbazone could be prepared, and the base was unchanged by boiling acetic anhydride. It was recognised that the methyl iodide was a source of a trace of catalytic iodine, and the brucidine analogue was obtained by the use of methanol and a crystal of iodine (Gulland, Perkin, and Robinson, J., 1927, 1643).

In a later paper (Achmatowicz, Perkin, and Robinson, J., 1932, 495), the oxidation of methoxymethyl dihydroneostrychnidine by means of potassium permanganate in acetone solution was studied. The product was an acetone compound of the oxymethoxy dihydroneostrychnidine-C, m.p. 305–306°. The opinion was expressed that (C) is (B) in purer form.

An interesting observation was the conversion of the isomeride-C into oxymethyl neostrychnidinium salts by boiling it with 20% sulphuric acid. The iodide was analysed, and the related chloride could be converted into the base-C by the action of methanolic potassium hydroxide. This was regarded as a proof that the oxygen taken up is not present in a labile group such as an ethylene oxide.

Our further observations suggest that these so-called isomerides are either very labile isomerides or owe their differing melting points to the presence of tenaciously held solvent.

Material of m. p. 285°, corresponding to isomeride-B, afforded a *p*-nitrophenylhydrazone which could not, however, be fully purified by crystallisation. It gave the characteristic colour reaction of its class with aqueous alcoholic sodium hydroxide.

The bases of m. p. 210–224° (A) and m. p. 285° (B) were converted in the known manner in oxynestrychnidine methiodide; the same product was obtained in each case and it tallied with the description (*loc. cit.*) of the salt from isomeride-C. On treatment with methanolic potassium hydroxide the latter base was produced.

An indication that the skeleton was unaltered by the oxidation was afforded by reduction of isomeride-B under Clemmensen's conditions with formation of methoxymethyl tetrahydrostrychnidine. These results suggest that the oxidation product is an aldehyde or ketone, and we propose the replacement of the prefix "oxy" by "oxodihydro". Methoxymethyl dihydroneostrychnine is found to be convertible into oxodihydromethoxymethyl dihydroneostrychnine either by leaving a methanolic solution containing a trace of iodine to evaporate in the air, or by boiling with methanol and methyl iodide. The use of ethanol led to the formation of an uncrystallisable gum. The new base holds firmly $\frac{1}{2}$ MeOH or $\frac{1}{2}$ EtOH. Although it certainly forms a *p*-nitrophenylhydrazone, this derivative showed no tendency to crystallise. The base was also oxidised by means of ferric chloride in *N*-hydrochloric acid. The crystalline product appears to have the composition $C_{44}H_{56}O_7N_8$, that is, two molecules of the base take up one atom of oxygen. A low value was obtained for the molecular weight in fused camphor, but this is probably due to fission of the molecule under the conditions of the experiment. A very satisfactory oxidation of nestrychnine occurs when its acid solution is treated with bromine water in the cold. The *hydrobromide* of oxodihydronestrychnine* crystallises in high yield. The free base exhibits interesting properties and transformations which will be described in detail in a subsequent communication. It is mentioned here because the composition change is the same as that observed in other cases and because this substance is the most characteristic of the oxodihydroneo-bases which we have encountered.

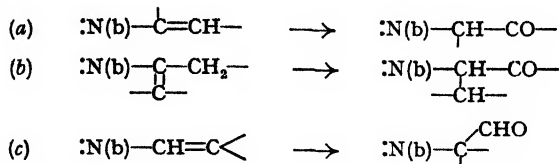
Although this and the other oxodihydro-bases reduce ammoniacal silver solutions with ease and slowly reduce Fehling's solution, it does not follow that they are aldehydes. It is well known that many α -amino-ketones are readily oxidised by the reagents mentioned.

The aldehyde hypothesis seems to be inconsistent with the reduction of oxodihydromethoxy-

* The use of *neo* in this name may be superfluous because dihydroneostrychnine is dihydrostrychnine. But this depends on the validity of our views and the *neo* is retained in order to show the origin of the base.

methylneostrychnidine to methoxymethyltetrahydrostrychnidine and with the formation of oxodihydromethoxymethylstrychnidine-C from oxodihydromethylstrychnidinium salts by the action of such a vigorous reagent as methyl alcoholic potassium hydroxide.

The only rational explanations of the formation of these oxodihydroneo-bases that we can devise are as follows :



Added May 9th, 1947.—It now seems probable that oxodihydroneostrychnidine is not analogous to the other oxo-compounds mentioned herein, and the discussion is therefore postponed.

Added November 9th, 1947.—It has been established that the salt first formed is a neo-strychnine dibromide (one bromidion) which changes to oxodihydroallostrychnine hydrobromide in warm aqueous solution. The free base is an aldehyde produced in accordance with hypothesis (c). A statement of these relations was made to the Organic Chemistry Section of the International Congress of Chemistry (London, 1947).

EXPERIMENTAL.

Oxodihydromethoxymethyldihydroneostrychnidine.—This substance was obtained by the known method (*loc. cit.*, 1927) and had variable m. ps. ranging from 210° to 224° (lit. 235°) in different runs. After addition of methanol to a solution in pyridine, the crystals that separated had m. p. 285° and the same value was reached by refluxing the initial product with ethanol or acetone. Only a small quantity of dark material remained in the filtrate.

Oxidation of methoxymethyldihydroneostrychnidine (7 g.) by means of potassium permanganate in acetone solution (*loc. cit.*, 1932) gave 0.5 g. of the variety, m. p. 305°. This separated on concentration of the acetone solution, and the bulk of the product was obtained on removal of the solvent as an uncrystallisable oil. It is very difficult to determine whether the varieties, m. p. 285° and m. p. 305°, are identical or not. The mixed m. p. was 288—294°, and when a pyridine solution of the base, m. p. 285°, was mixed with methanol containing a few crystals of the base, m. p. 305°, the separated crystals had m. p. 304—306°. On the other hand the variety, m. p. 285°, can be recrystallised without change of m. p. and no change of m. p. was observed on refluxing it with acetone, alone or in presence of a little sodium hydroxide. Conversion of any of the supposed isomerides into oxymethylneostrychnidine methiodide (*loc. cit.*) gave one and the same salt, m. p. 232—234° (lit., 238—240°) showing undepressed mixed m. ps.

The quaternary chloride from the variety, m. p. 285°, was treated with methanolic potassium hydroxide in the known manner and afforded a base, m. p. 298—300°, m. p. 300—302° on admixture with the variety, m. p. 305°.

A mixture of the variety, m. p. 285° (0.1 g.), *p*-nitrophenylhydrazine (0.04 g.), and acetic acid (2 c.c.) was heated on the steam-bath for ½ hour. Addition of aqueous ammonia precipitated a light yellow amorphous solid which was purified by solution in hot ethanol and addition of water; it could not be crystallised (Found : C, 67.9; H, 7.0. $\text{C}_{20}\text{H}_{28}\text{O}_4\text{N}_2$ requires C, 67.3; H, 6.8%). The substance softened at 120° and decomposed at 185—186° but these figures have little significance. Its alcoholic solution developed an intense red coloration on the addition of a drop of 10% aqueous sodium hydroxide, the reaction characteristic of *p*-nitrophenylhydrazones. Its acid solution developed a carmine coloration (strychnidine reaction) on addition of ferric chloride. The variety, m. p. 305°, gave a similar *p*-nitrophenylhydrazone exhibiting these reactions.

A mixture of the variety, m. p. 285° (2.0 g.), concentrated hydrochloric acid (5 c.c.), water (4 c.c.), and amalgamated zinc (5 g., prepared according to "Organic Reactions," 1, 163) was refluxed for 12 hours with the addition of further concentrated hydrochloric acid (1 c.c.) each hour. The diluted solution was basified with sodium hydroxide and the product obtained as a white solid (1.8 g., m. p. 220—221°). The substance was crystallised from benzene and from pyridine-methanol and identified as methoxymethyltetrahydrostrychnidine by observation of the m. p. 220—221°, undepressed on admixture with an authentic specimen.

Oxodihydromethoxymethyldihydroneostrychnine.—Methoxymethyldihydroneostrychnine was prepared from methylstrychnine by the method of Achmatowicz, Clemo, Perkin, and Robinson (*J.*, 1932, 769), and a consistent yield of about 75% was secured by a modification of procedure of isolation. After the removal of methanol and addition of water the alkaline solution was mixed with crushed ice and gradually acidified by acetic acid in a funnel with shaking with ether. In this way the formation of gummy by-product was avoided.

(A). Methoxymethyldihydroneostrychnine (5 g.) was dissolved in hot methanol (300 c.c.) and a small crystal of iodine added. The solution was allowed to evaporate in the air for a week. Gum was separated from the sparingly soluble crystalline crust by treatment with hot methanol, the solid was collected, and the filtrate allowed to evaporate again. By repetition of this process the yield was 1.8 g. The substance separated from pyridine-methanol as a jelly which became crystalline on warming. It is sparingly soluble in ethanol, and when the solutions were quickly cooled a gel was also formed; on slow cooling, however, the substance separated as radiating cluster of fine needles, which shrank at 225°.

m. p. 275—277° on slow heating. If heated rapidly the m. p. ranges from 230° to 240° (Found in material dried over sulphuric acid: C, 68.6; H, 7.1; N, 6.7; MeO, 11.3. $C_{23}H_{28}O_3N_2 \cdot 0.5EtOH$ requires C, 68.7; H, 7.4; N, 6.7%; 1 MeO + 0.5 EtO, Calc. as MeO, 11.1%). When ethanol was employed in this preparation no crystallisable product was obtained. The base dissolves slowly but completely in *n*-hydrochloric acid and is precipitated by the addition of sodium acetate. It forms a *p*-nitrophenylhydrazone and a 2:4-dinitrophenylsemicarbazone, but neither of these derivatives could be crystallised. The former gave an intense orange-red coloration, blue-tinged in thin layers, on the addition of potassium hydroxide to its alcoholic solution.

(B). Methoxymethylidihydroneostrychnine (4 g.) was refluxed with methyl iodide (5 c.c.) and methanol (40 c.c.) for 3 hours and then shaken in contact with air for 10 days. The separated crystals (0.6 g.) were deposited from pyridine solution by the addition of methanol as a jelly which crystallised on keeping. This specimen softened at 222°, m. p. 275—277° (Found: C, 68.5; H, 6.9. $C_{23}H_{28}O_3N_2 \cdot 0.5MeOH$ requires C, 68.4; H, 7.3%). Recrystallised from ethanol (gel \rightarrow crystals) it was obtained in needles, softening at 240°, m. p. 275—277°, and mixed with the product from (A) it softened at 235°, m. p. 275—277°. It is quite possible that the half molecule of solvent is in combination in the form $-\dot{C}(OR)-O-\dot{C}(OH)-$ and that the variations of softening points are due to incomplete exchange of R by R'. When iodine (0.2 g.) was used in place of methyl iodide in this procedure, the yield was 1.0 g. The *p*-nitrophenylhydrazone shrank at 130°, m. p. 155—157° (decomp.). Strychnine and methoxymethylidihydroneostrychnine immediately decolorise permanganate in very dilute sulphuric acid solution. Oxodihydroneostrychnine is very slowly attacked under these conditions.

Reduction according to Clemmensen afforded a base, m. p. 261—262°, readily soluble in methanol, but the investigation of this substance has not yet been completed.

Oxidation of Methoxymethylidihydroneostrychnine by Means of Ferric Chloride.—A cold solution of ferric chloride (3.3 g., anhydrous) in water (15 c.c.) was added to one of methoxymethylidihydroneostrychnine (3.8 g.) in *n*-hydrochloric acid (35 c.c.). After an hour the red solution was basified with ammonia, precipitating the base along with ferrous hydroxide. The whole was shaken with ethyl acetate (about 50 c.c.), filtered, and the ester layer separated and evaporated (2.6 g. of crystalline residue). The substance is very sparingly soluble in hot methanol or ethanol, readily soluble in dilute hydrochloric acid. It crystallises from chloroform on the addition of ether in small, flat needles, m. p. 190° (Found: C, 70.9; H, 7.1; N, 7.3; *M* (Rast in camphor), 467. $C_{23}H_{28}O_3N_4$ requires C, 71.1; H, 7.2; N, 7.2%; *M*, 776]. The composition suggests a compound of oxodihydroneostrychnine, $C_{23}H_{28}O_3N_2$, and methoxymethylidihydroneostrychnine, $C_{23}H_{28}O_3N_2$, but the substance does not afford a *p*-nitrophenylhydrazone and it gives no precipitate on the addition of *p*-nitrobenzenediazonium chloride to an acid solution. Possibly it is an ether, and the composition $C_{46}H_{56}O_7N_4$ (Calc.: C, 71.3; H, 7.0; N, 7.2%) is not excluded.

Oxodihydroneostrychnine.—A hot solution of neostrychnine (8.35 g.) in 1.5*N*-sulphuric acid (110 c.c.) was cooled to the room temperature and 0.2*N*-bromine water (250 c.c.) added in 4 to 5 portions with shaking, so that the yellow perbromide that separated was quickly decomposed. The white crystalline precipitate was collected after 15 minutes, washed with a little water, and dried in a vacuum desiccator (9.8 g.). The salt is a hydrobromide free from sulphate. Although very sparingly soluble in cold water, it dissolves readily on heating and forms supersaturated solutions. Crystallisation is best effected from concentrated solutions and seeding is necessary. The colourless, well-shaped prisms become deep red with shrinkage at 170° and gradually decompose on further heating (Found: C, 55.2, 56.0; H, 5.6, 5.7; Br, 17.3, 18.7. $C_{21}H_{22}O_3N_2 \cdot HBr \cdot H_2O$ requires C, 56.1; H, 5.6; Br, 17.8%). The free base was obtained as a chalky precipitate on addition of ammonia to a cold solution of the hydrobromide. It was collected, washed, and dried in a vacuum (7.5 g., m. p. 80—140°). This product was dissolved in methanol (80 c.c.) and the solution concentrated to 15—20 c.c. when it separated in stellate clusters of transparent prisms (6 g.), m. p. 128° (decomp.) (Found: C, 69.1; H, 6.9; N, 7.4. $C_{21}H_{22}O_3N_2 \cdot MeOH$ requires C, 69.1; H, 6.8; N, 7.3%). The solvent is lost slowly at 100°, more rapidly at near 120° (loss, 7.6. Calc.: 8.3%). The solvent-free base has m. p. 190° and is hygroscopic (Found: C, 71.6; H, 6.4; N, 7.9. $C_{21}H_{22}O_3N_2$ requires C, 72.0; H, 6.3; N, 8.0%).

It is of interest that oxodihydroneostrychnine can also be obtained, although in poor yield, by aerial oxidation of neostrychnine in methanol containing iodine. A mixture of neostrychnine (3 g.), methanol (120 c.c.), and iodine (0.2 g.) was shaken for 9 days under air. Some neostrychnine remained undissolved (1.8 g., m. p. 224—225°) and the filtrate was evaporated and the residue extracted with dilute sulphuric acid. Ammonia precipitated a white solid (0.5 g., m. p. 110° with frothing) and this was converted into the semicarbazone hydrochloride in the usual manner. The salt, when slowly heated, darkened at 240° and decomposed at 255°, and the behaviour was unchanged on admixture with the derivative prepared from oxodihydroneostrychnine. The base is sparingly soluble in the simple alcohols but has a tendency to form supersaturated solutions. It is readily soluble in chloroform and can easily be crystallised by addition of ether to a concentrated solution. It is fairly soluble in dilute hydrochloric acid. A silver mirror is formed with ammoniacal silver nitrate after heating on the steam-bath for 10 minutes, and the base also reduces silver oxide in boiling alcoholic suspension, forming a mirror. It slowly reduces Fehling's solution on heating. The Otto reaction (60% sulphuric acid) is a transient violet coloration changing to deep red and finally brown. The *p*-nitrophenylhydrazone is a yellow solid, the alcoholic solution of which becomes deep red on the addition of aqueous sodium hydroxide. Crystalline derivatives showing the presence of a carbonyl group have been prepared and analysed, but a description of these is reserved for a future communication.

The authors are grateful to the Trustees of the Palit Fund, Calcutta University, for a Scholarship awarded to one of them (R. N. C.), and also to the University of Melbourne and the Carnegie Fund for a Travelling Scholarship and a Grant, respectively, awarded to another of them (K. H. P.).

305. Strychnine and Brucine. Part XLVIII. Degradation of the Strychnineacetic Acid prepared from Pseudostrychnine.

By K. H. PAUSACKER and SIR ROBERT ROBINSON.

The alkaline degradation of strychnineacetic acid has been studied in the hope of supplying evidence in favour of one of the two structures discussed in Part XLII (Briggs, Openshaw, and Robinson, *J.*, 1946, 903). One of the products should be 3- or 4-methylcarbazole, and an unequivocal result would have been of great value. Actually the main constituent of the carbazole fraction was carbazole itself, but infra-red absorption analysis, carried out by Mr. R. E. Richards of the Physical Chemistry Laboratory, Oxford University, showed that 3-methylcarbazole, but no 4-methylcarbazole, was present in small relative amount.

The carbazole from strychnine was found to contain a trace of 3-methylcarbazole, and degradation of the product of interaction of oxodihydroneostrychnine and methylmagnesium iodide afforded a carbazole fraction containing 3-methylcarbazole and an unidentified substance.

For the study of the infra-red absorption 1-, 2-, and 3-methylcarbazoles were prepared by known methods.

4-Methylcarbazole does not appear to have been hitherto described and was synthesised without ambiguity from 4-chloro-*m*-tolylhydrazine by way of a related tetrahydrocarbazole.

CARBAZOLE was first obtained from strychnine by dry distillation and by heating with zinc dust (Lobisch and Schoop, *Monatsh.*, 1886, 7, 614); by heating strychnine with soda-lime, Lobisch and Malfatti (*ibid.*, 1888, 9, 626) obtained carbazole, skatole, and β -picoline. The formation of carbazole was confirmed by Clemo, Perkin, and Robinson (*J.*, 1927, 1625), who decomposed methylstrychnine at 150–200°. Such drastic degradations affording aromatic compounds of high intrinsic stability are admittedly of problematic value in constitutional studies, but it occurred to us that the survival of a group introduced into the strychnine molecule would be significant.

It is known that pseudostrychnine (hydroxystrychnine) contains N(b)C(OH) (Blount and Robinson, *J.*, 1932, 2305), and Leuchs (*Ber.*, 1943, 76, 1068) showed that this base condenses with malonic acid to strychnineacetic acid, $\text{N(b)C}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, which loses carbon dioxide with formation of methylstrychnine.

Degradation of a crude product obtained in this way gave a carbazole fraction which on examination by the usual methods was found to contain methylcarbazoles in considerable relative amount (up to 40%). At this point we were fortunate to receive the valuable co-operation of Mr. R. E. Richards to whom we express our gratitude. He examined the infra-red spectra of carbazole and the four *C*-methylcarbazoles and noted the presence of certain characteristic bands. He also studied our degradation products and synthetic mixtures of carbazole and the various isomerides. The degradation product was found to contain from 5 to 12% of 3-methylcarbazole, and 4-methylcarbazole was absent.

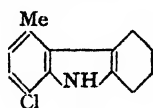
As a control we degraded strychnine by the same method, and the infra-red analysis of the product showed that it was carbazole containing a little (<1%) 3-methylcarbazole. As the 3-position is *para* to the imino-group it would not be surprising if a small amount of the homologue were synthesised by condensation reactions in the course of the process. It was also shown that a mixture of 4-methylcarbazole and carbazole afford no 3-methylcarbazole under the conditions employed, although naturally it would never be feasible to eliminate the possibility of migration of groups at an earlier stage.

Up to this point it seemed safe to conclude that N(b) is attached to position 3 of a partly reduced carbazole nucleus in the strychnine molecule. We hoped to clinch the matter by introducing a methyl group in a different position, and for this purpose selected oxodihydroneostrychnine (see the preceding paper) as the starting point. This base probably contains $\text{N(b)C}\cdot\text{CO}$, and reaction with methylmagnesium iodide should result in attachment of methyl to the β -carbon with respect to N(b). Hence the result of degradation was expected to be 4-methylcarbazole (or 2-methylcarbazole). The outcome was surprising since the carbazole fraction of the degradation product contained about 10% of 3-methylcarbazole as found by infra-red absorption analysis. Unidentified substances were also present. Now whatever the constitution of strychnine may be, it is anomalous that these two degradations should have given the same result. It is inescapable that migration must have occurred in one of the cases unless, indeed, the methyl group of 3-methylcarbazole does not arise from that introduced into the strychnine molecule. It will be seen that the clarity of an argument that could be developed is obscured by the necessity to exercise judgment in the interpretation of the results.

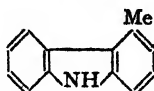
Synthesis of 4-Methylcarbazole.—According to Plancher and Carrasco [*Roy. Acad. Lincei*, 1904, (V), 18, (i), 632, cited by Hollins, "Synthesis of Nitrogen Ring Compounds," p. 168] the

Fischer reaction applied to 3-methylcyclohexanone phenylhydrazone affords a mixture of 2- and 4-methyltetrahydrocarbazole; Borsche, Bothe, and Witte (*Annalen*, 1908, 359, 61) found only the 2-methyl derivative. (Owing to a special numbering system this is described as the 4-methyl derivative, but it gives 2-methylcarbazole on dehydrogenation.) To effect an unambiguous synthesis it was preferable to start with a *m*-tolylhydrazine, and we blocked the 4-position by a chlorine atom.

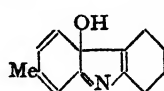
4-Chloro-*m*-toluidine (Gattermann and Kaiser, *Ber.*, 1885, 18, 1600) was converted in the usual manner into the hydrazine and then into 8-chloro-5-methyl-1:2:3:4-tetrahydrocarbazole



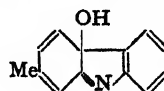
(I.)



(II.)



(III.)



(IV.)

(I) by heating with dilute sulphuric acid; a by-product is discussed below. (I) was dehydrogenated by chloranil with formation of 1-chloro-4-methylcarbazole and converted into 4-methylcarbazole (II) by heating with palladised charcoal in a stream of hydrogen.

The by-product mentioned above contained a trace of chlorine and hence gave low results for carbon. It appears, however, to be $C_{13}H_{11}ON$. It was dehydrogenated by palladised charcoal to a substance $C_{13}H_{11}ON$ which gave sharp results on analysis. These curious compounds are devoid of phenolic character and do not form picrates. The constitutions (III) and (IV) are suggested provisionally. It is hoped that an opportunity to make a further examination of these substances will be found.

Added in Proof (November 9th, 1947).—We now know that oxodihydroneostrychnine is a derivative of allostrychnine and is an aldehyd. The methyl introduced by the Grignard reagent is remote from the carbazole nucleus. Therefore the formation of 3-methylcarbazole is probably due to rearrangement or synthesis in the course of the degradation process.

EXPERIMENTAL.

Degradation of Strychnineacetic Acid.—Pseudostrychnine was prepared by the elegant method of Leuchs (*Ber.*, 1940, 73, 734) who states that strychnine (100 g.) yields crude pseudostrychnine (41–43 g.), neutral product (10–15 g.), and unchanged strychnine (30–33 g.). Our experience of several runs is that the respective average figures are 54, 20, and 4.

This crude pseudostrychnine (43 g.) was converted into strychnineacetic acid (Leuchs, *loc. cit.*) by condensation with malonic acid. The isolated perchlorate was powdered with animal charcoal and extracted with water in a Soxhlet apparatus (39 g.). On treatment with *N*-sodium bicarbonate solution (69 c.c.) and continuous extraction with chloroform, strychnineacetic acid (30 g.) was obtained. This was then heated in batches (6 g.) for 0.5 hour at 280–300°; a brown powder (25 g.) was obtained. Leuchs (*Ber.*, 1943, 76, 1069) claims that methylstrychnine can be obtained in 17–25% yield by this method. This was powdered in 5 g. lots with soda-lime (30 g.) and heated in a metal-bath at 380–400° for 1 hour. The distillate, a brown tar, was extracted with benzene, washed with acid and alkali and steam-distilled. After about 10 l. had distilled, no further volatile substances came over. The distillate was extracted with benzene, concentrated, and passed through an alumina column. The first washings were found to be light yellow and fluorescent in ultra-violet light. These were concentrated and the resultant crystals were recrystallised from light petroleum (b. p. 60–80°). After sublimation in a high vacuum at 160°, a white solid (30 mg.) was obtained. It had a faint indolaceous odour, m. p. 203–207° after shrinking at 199° (Found: C, 86.0; H, 5.9; C-Me, 3.7%). On being kept in the air it became light brown. When this substance (3 mg.) was treated with picric acid (3.6 mg.) in benzene, a red-brown picrate, m. p. 156–162°, was obtained. The white solid dissolved in concentrated sulphuric acid to a very pale yellow solution which became ultramarine blue on the addition of a drop of concentrated nitric acid. When it was dissolved in alcohol and an acid solution of *p*-nitrobenzenediazonium chloride added, a bright yellow coloration developed. Infra-red measurements indicate that the mixture contains about 8–12% of 3-methylcarbazole along with carbazole. None of the other methylcarbazoles were detected but a small amount of some impurity was also found to be present.

The following experiments were made for comparative purposes.

Carbazole. When recrystallised from benzene the specimen employed had m. p. 238° (Found: C-Me, 0.85. Calc.: C, 86.2; H, 5.4; C-Me, 0.0%). The yellow solution in concentrated sulphuric acid became ultramarine blue on the addition of a drop of concentrated nitric acid. Its solution in alcohol became pale pink on the addition of an acidified solution of *p*-nitrobenzenediazonium chloride. The picrate (bright red) had m. p. 183–184°; mixed m. p. with the unknown picrate, 157–160°. The melting points of mixtures of carbazole and 3-methylcarbazole, and of carbazole and 4-methylcarbazole are shown below:

Carbazole and 3-methylcarbazole.

Carbazole, %	4	16	27	38	52	62	79	89	95
Softening pt.	200°	198°	198°	203°	210°	213°	220°	228°	234°
M. p.	200—	199—	201—	205—	212—	214—	224—	231—	237—
	202°	201°	203°	207°	214°	217°	227°	233°	238°

Carbazole and 4-methylcarbazole.

Carbazole, %	4	13	24	36	53	62.5	75	87.5	94.5
Softening pt.	110°	110°	107°	117°	130°	175°	190°	224°	230°
M. p.	112—	113—	115—	140—	168—	198—	214—	228—	235—
	117°	117°	150°	174°	196°	220°	224°	232°	236°

A mixture of the unknown with an equal quantity of a 3-methylcarbazole-carbazole mixture (60 : 40) softened at 198° and had m. p. 202—205°.

3-Methylcarbazole. The specimen had m. p. 202° (Found: C-Me, 6.0. Calc.: C, 86.2; H, 6.1; C-Me, 8.3%). It gave a colourless solution in concentrated sulphuric acid which turned emerald green upon the addition of a drop of concentrated nitric acid. Its alcoholic solution became faintly yellow upon the addition of *p*-nitrobenzenediazonium chloride. The dark red picrate had m. p. 178—179°; mixed m. p. with the unknown picrate, 155—158°; mixed m. ps. with carbazole picrate were 158—162° (33% carbazole picrate), 160—164° (50%), 160—164° (66%).

A mixture of carbazole (20 mg.) and 3-methylcarbazole (20 mg.) could not be separated by chromatography under the conditions employed.

4-Methylcarbazole (Found: C-Me, 5.7%). The colourless solution in sulphuric acid became ultramarine blue on the addition of nitric acid. Its alcoholic solution gave a yellow-brown coloration with *p*-nitrobenzenediazonium chloride.

From these results it appears that the degradation product contains a compound, affording acetic acid in the Kuhn-Roth estimation of side-chain methyl, other than the 10% of 3-methylcarbazole indicated by the infra-red analysis. The faint indolaceous odour and the colour reactions suggest that this may be an indole derivative, but the possibility of the presence of higher homologous carbazoles cannot be dismissed.

The residue in the flask from the degradation reaction was found to contain a fluorescent acid substance. It gave the carbazole reaction with sulphuric-nitric acid but was obtained in such small quantity that further examination was precluded. When strychnine was distilled over soda-lime at 400°, carbazole, m. p. 229—232°, could be isolated in the manner described above. The specimen had the usual faint indolaceous odour and became light brown in colour on being kept for a few days. The infra-red spectrum showed strong carbazole bands at 845 cm.⁻¹ and 857 cm.⁻¹, a weak band at 810 cm.⁻¹ (3-methylcarbazole, <1%), and a very weak band at 787 cm.⁻¹, which was not found with carbazole or any of the four C-methylcarbazoles. A mixture of carbazole (60 mg.) and 4-methylcarbazole (40 mg.) was heated with soda-lime (30 g.) for an hour at 380—400°. The distillate was collected by means of acetone and sublimed, m. p. 192—217°; carbazole-4-methylcarbazole (62.5 : 37.5), m. p. 198—220°. Infra-red examination showed the presence of carbazole and 4-methylcarbazole, but the absence of 3-methylcarbazole could not be categorically affirmed because 4-methylcarbazole has a band at 812 cm.⁻¹ in the vicinity of that of 3-methylcarbazole at 808 cm.⁻¹. However in the graph obtained there was no appreciable broadening of the 812 band towards 808.

ββ-N(b)-Hydroxymethylidihydroneostrychnine.—A Grignard solution was prepared from magnesium (13 g.), methyl iodide (23.5 c.c.), and ether (300 c.c.); after the addition of anisole (200 c.c.), the ether was distilled (bath at 100°). A solution of oxodihydroneostrychnine (28.5 g. of the base, 1 MeOH) in anisole (350 c.c.) was added and the whole heated for 5 hours at 100°. After being poured on ice, the product was extracted by dilute hydrochloric acid and the solution basified with ammonia (dried as a light yellow solid, 27.5 g.). A portion was crystallised from alcohol (charcoal) and from benzene-light petroleum (b. p. 80—100°) and obtained as prismatic needles, which shrank at 130°, m. p. 160° (decomp.) (Found: C, 72.5; H, 7.2. C₂₂H₂₂O₂N₂ requires C, 72.1; H, 7.1%). This base (5 g., crude) was ground with soda-lime (25 g.) and distilled at 400°, and the product from five such batches was worked up in the manner already described. The carbazole fraction had m. p. 116—200°. The infra-red spectrum showed strong bands at 810 cm.⁻¹ (3-methylcarbazole, ca. 10%), the carbazole bands at 845 cm.⁻¹ and 857 cm.⁻¹, and a very weak band at 787 cm.⁻¹ (see above). The absence of 4-methylcarbazole is not established owing to the possible swamping of its relatively weak characteristic bands by stronger neighbouring absorption due to carbazole and 3-methylcarbazole. The low m. p. suggests the presence of 4-methylcarbazole or of some other unidentified constituent.

4-Chloro-*m*-tolylhydrazine.—A hot solution of 4-chloro-*m*-toluidine (5.8 g.) in dilute hydrochloric acid (67 c.c. containing 11 c.c. of concentrated acid) was added to concentrated hydrochloric acid (107 c.c.), cooled to 0°, and diazotised by addition of sodium nitrite (3.2 g.) dissolved in a little water. The diazo-solution was poured into an ice-cold solution of stannous chloride (21 g.) in concentrated hydrochloric acid (26 c.c.). After an hour at 0° the mixture was kept for 12 hours at the room temperature, the solid collected, washed with saturated brine, and triturated with a solution of sodium hydroxide (17 g.) in water (50 c.c.). The base was collected, washed with water, and dried (3.8 g. or 59%). The substance crystallised from water in needles, m. p. 61° (Found: C, 53.5; H, 5.6. C₉H₈N₂Cl requires C, 53.7; H, 5.8%). A mixture of cyclohexanone (2.4 g.), 4-chloro-*m*-tolylhydrazine (3.6 g.), and ethanol (10 c.c.) was refluxed for an hour and added to water. The product was isolated by means of ether (yield, 4.8 g.), and it crystallised from alcohol in plates, m. p. 58°.

The crude cyclohexanone 4-chloro-*m*-tolylhydrazone (from 5.7 g. of chlorotolylhydrazine) was boiled with a mixture of concentrated sulphuric acid (10 c.c.) and water (90 c.c.) for 5 minutes; chloride ion was detected in the aqueous solution. The red oil was extracted with ether leaving a pink solid (0.35 g.) which crystallised from alcohol in dark red needles, m. p. 195—197° (decomp.), and contained nitrogen and chlorine (Found: C, 66.0; H, 4.9; N, 6.1%). The nature of this compound has not been discovered. The oil from the ethereal extract was distilled, b. p. 222—223°/20 mm. (5.7 g.), and treated with light petroleum (b. p. 40—60°). An insoluble white solid residue (0.7 g.) crystallised from aqueous alcohol (charcoal) in white needles, m. p. 199—201° (decomp.) [Found: C, 76.8; H, 7.4; N, 6.9; *M* (Rast in camphor), 220. C₁₃H₁₁ON requires C, 77.6; H, 7.5; N, 7.0%; *M*, 201]. The low percentage of carbon found is due to a trace of chlorine the presence of which was shown by the Beilstein test. This compound

(A) will be further examined. The light petroleum solution was concentrated and afforded 5.0 g. of a pale yellow solid. Recrystallisation from aqueous ethanol gave colourless needles, m. p. 64.5° (Found: C, 70.4; H, 6.5. $C_{13}H_{11}NCl$ requires C, 71.0; H, 6.4%). When the specimens of this 8-chloro-5-methyl-1:2:3:4-tetrahydrocarbazole (I) were examined after a lapse of months, in order to repeat the analysis, it was found that they had decomposed with formation of dark resins.

4-Methylcarbazole (II).—Chloromethyltetrahydrocarbazole (0.5 g.) and palladised charcoal (0.15 g.) were heated (bath at 280–300°) in a stream of hydrogen; evolution of hydrogen chloride ceased after 2 hours.

The mass was extracted with acetone and the methylcarbazole precipitated by addition of water (0.38 g.). The compound crystallised from aqueous ethanol as small white needles, m. p. 115–116° (Found: C, 85.8; H 6.2. $C_{13}H_{11}N$ requires C, 86.1; H, 6.1%). The picrate, m. p. 160.5°, separated from benzene in red needles (Found: C, 56.0; H, 3.6. $C_{13}H_{11}O_7N_4$ requires C, 55.6; H, 3.4%). Other properties of 4-methylcarbazole are mentioned above.

When the compound (A), $C_{13}H_{11}ON$, was similarly dehydrogenated, 0.33 g. gave 0.25 g. of solid material. This crystallised from aqueous ethanol as white needles, m. p. 262° (decomp.) [Found: C, 79.2; H, 5.8; N, 7.2; *M* (Rast in camphor), 195. $C_{13}H_{11}ON$ requires C, 79.2; H, 5.6; N, 7.1%; *M*, 197]. This substance is isomeric with a methylphenoxazine, but phenoxazine has m. p. 156° and 2-methylphenoxazine has m. p. 123–125°, so that it is unlikely to be 3-methylphenoxazine. The only alternative we can suggest is, (IV) whence the tetrahydro-derivative (A) should be (III). The stability of these substances is noteworthy.

1-Chloro-4-methylcarbazole.—Chloromethyltetrahydrocarbazole (1.5 g.) was oxidised by chloranil in xylene according to the method of Barclay and Campbell (*J.*, 1945, 530). The resultant dark oil afforded a picrate (2.1 g.) which crystallised from benzene in dark red needles, m. p. 154.5° (Found: C, 51.7; H, 3.3. $C_{13}H_{11}O_7N_4Cl$ requires C, 51.3; H, 2.9%). The chloromethylcarbazole crystallised from aqueous ethanol in slender, white needles, m. p. 70° (Found: C, 71.6; H, 4.4. $C_{13}H_{11}NCl$ requires C, 72.4; H, 4.7%).

The authors thank the University of Melbourne for a travelling Scholarship and the Carnegie Fund for a grant awarded to one of them (K. H. P.).

They are greatly indebted to Mr. R. E. Richards for his reports on the infra-red absorption spectra.

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[Received, January 29th, 1947.]

306. Thermal Decomposition of Explosives in the Solid Phase. Part I. The Thermal Decomposition in a Vacuum of Certain Mono- and Dinitrobenzenediazo-oxides, with a Note on the Kinetics of Thermal Breakdown of 2-Nitrobenzene-4-diazo-1-oxide.

By J. VAUGHAN and L. PHILLIPS.

The rates of decomposition, in a vacuum, of certain nitrobenzenediazo-oxides have been studied between 50° and 120°. Under these conditions mononitrobenzene-2-diazo-1-oxides appear to be less stable than the corresponding 4-diazo-1-oxides. A similar conclusion applies to the dinitrobenzenediazo-oxides. This is probably due to restricted resonance in the 2:1-diazo-oxides owing to proximity of electrostatic charges. Substitution of nitro-groups in positions *o*- or *p*- to the oxygen atom in 2:1-diazo-oxides leads to an increased stability; substitution in the *m*-position appears to be without effect. Similar effects are observed with *o*-substitution on the 4:1-diazo-oxides. These effects can be explained on electronic considerations. The kinetics of thermal decomposition of 2-nitrobenzene-4-diazo-1-oxide have been investigated. The results are in agreement with the theory of solid-phase decomposition put forward by Prout and Tompkins (*Trans. Faraday Soc.*, 1944, 40, 488).

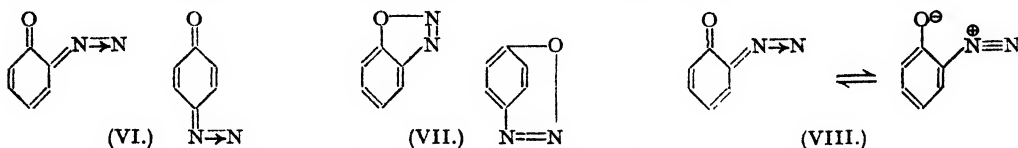
THE following five aromatic diazo-oxides were examined for thermal stability characteristics: 4- (I) and 5-nitrobenzene-2-diazo-1-oxide (II), 2-nitrobenzene-4-diazo-1-oxide (III), 4:6-dinitrobenzene-2-diazo-1-oxide (IV), 2:6-dinitrobenzene-4-diazo-1-oxide (V).

The method used for following the progress of decomposition was essentially that described by Farmer (*J.*, 1920, 117, 1432) in which the compound was allowed to decompose in a vacuum and the course of breakdown followed by means of the gas evolution-time curve. The temperature range covered was 50–120°, and the curves obtained in all cases were sigmoid in shape. Addition of the solid end-products did not result in any acceleration of the breakdown, and the gaseous products were also without catalytic effect. The gaseous products of decomposition of these diazo-oxides consist mainly of nitrogen, nitric and nitrous oxides, and carbon dioxide. Since the nitro-groups of mono- and di-nitrobenzene are comparatively stable at temperatures below 120°, the main process in the thermal decomposition of these diazo-oxides would seem to be fission of the diazo-nitrogen, together with some slight secondary reactions depending on the temperature of decomposition. The failure in all cases to obtain 1 mol. of

nitrogen per mol. of diazo-oxide indicated that some coupling may have occurred with the formation of a relatively stable product.

Of the mononitrobenzene diazo-oxides, the 2-diazo-1-oxides (I) and (II) were considerably less stable thermally than (III), a 4-diazo-1-oxide. This characteristic was also demonstrated by the behaviour of the dinitrobenzene compounds, (V) being more stable than (IV). Results also pointed to the following facts: (a) when a nuclear nitro-group is in an *o*- or *p*-position to the oxygen of the diazo-oxide grouping, a stabilising effect is exerted on the molecule; (b) a nitro-group in the *m*-position appears to be without effect on the stability; (c) the presence of two nitro-groups situated as in (a) leads to a stabilising effect greater than that exerted by only one such group.

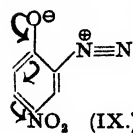
For many years there was considerable doubt as to whether these internal diazo-oxides had a quinonoid structure (VI) or contained an oxide ring (VII). It is, however, now evident that neither of these structures is correct and that the properties of such compounds are best explained on the basis of resonance hybrids, as in (VIII). This argument is reviewed by Hodgson and



Marsden (*J. Soc. Dyers Col.*, 1943, 59, 271), who point out that such a resonating system explains the superior stability of the diazo-oxides over the diazonium compounds. Thus the diazo-oxides are stabilised by their resonance energy, whilst the diazonium salts, not being resonating systems in this sense, are not stabilised in this manner.

Compounds (I), (II), and (III) can therefore be represented structurally by the general formulae shown in (VIII). The resonating energy of such systems is, by definition, greatest (*i.e.*, the greatest degree of stability is obtained) when both hybrids contribute equally to the equilibrium state of the molecule. Now in the "ionised" form of the 2:1-diazo-oxides, the negatively charged oxygen and the positively charged nitrogen are sufficiently close to set up an appreciable electrostatic attraction, so much so that resonance is probably to some extent inhibited. Consequently, the "ionised" form will preponderate, with the result that the resonance energy assumes a comparatively small value.

On the other hand, resonance in the 4:1-diazo-oxides should not be restricted to such an extent because of the greater separation of the electrostatic charges in the ionised form. Consequently, the resonance energy and therefore the stability of the 4:1-diazo-oxides should be greater than that of the corresponding 2:1-diazo-oxides, as has been found to be the case with (I), (II), and (III). Further support for this theory is afforded by the fact that (II) is less stable than (I). Both compounds are 2:1-diazo-oxides, the only difference being that the nitro-group is respectively in the *m*- and the *p*-position. Now, according to the electronic theory of organic



reactions, developed by Ingold *et al.*, the nitro-group is an electron-attracting group which exerts mesomeric effects in aromatic compounds. This effect would be expected to operate to reduce the fractional negative charge on the oxygen atom of the ionised form of (I), as in (IX), thereby decreasing the electrostatic attraction between the ionised groups. The contribution to the equilibrium state made by the non-ionised form therefore increases with consequent increase of resonance energy and therefore stability. Since this mesomeric effect cannot operate from a group in the *m*-position, (II) should be less stable than (I). This relative instability in (II) is enhanced by the fact that the nitro-group in (II) is in the *p*-position to the diazo-group. The electron-attracting nature of the nitro-group will tend therefore to increase the positive nature of the diazo nitrogen and will thus inhibit resonance by favouring the "ionic" structure of the molecule.

Introduction of a second nitro-group into the position ortho to the oxygen (where the mesomeric effect can again operate) should tend further to reduce the fractional charge on the oxygen atom. If the major contribution made to the stable structure before introduction of this second nitro-group still comes from the "ionised" form, this second nitro-group should tend to increase stability by bringing the stable structure nearer to the optimum condition, *i.e.* reducing the "amount" of ionised form. Conversely, it follows that if the introduction of a second nitro-group ortho to the oxygen atom in a mononitrobenzenediazo-oxide results in an increased stability, the "ionised" form must preponderate in the latter structure. Thus the fact that (IV) is more stable than (I) confirms that the "ionised" form of the latter preponderates

in the stable structure. Similarly, the fact that (V) is more stable than (III) indicates that, although (III) is more stable than (I), the ionised form still makes the greater contribution to the



relatively stable (III) structure. The destabilising effect of the adjacent charges in the 2 : 1-diazo-oxides is again illustrated by the fact that (IV) is less stable than the corresponding 4 : 1-diazo-oxide (V).

Kinetics and Mechanism of the Thermal Decomposition.—Investigation of the kinetics and mechanism of the thermal decomposition of nitrobenzenediazo-oxide was not the main object of this work. Attempts at kinetic interpretation have only been made, therefore, where data of sufficient accuracy are available. Furthermore, secondary processes other than elimination of diazo-nitrogen played a large part in the decomposition of dinitrobenzenediazo-oxide, so the kinetics were very complex. Satisfactory data were, however, available for compound (III).

The decomposition of all compounds studied in the present investigation is characterised by sigmoid volume-time curves, and microscopic examination of decomposition products indicates that decomposition probably occurs in the solid phase without the incidence of partial melting which can result in autocatalytic reactions. Considerable work has been carried out by Garner and other investigators during the last 15 years on the kinetics and mechanism of thermal decomposition in the solid phase. The position has been reviewed by Garner (*Trans. Faraday Soc.*, 1938, "Symposium on Solid Phase Reactions"; *Science Progress*, 1938—39, 33, 209), and more recently by Prout and Tompkins (*loc. cit.*), whose treatment of the problem appears to be most complete. Agreement is general that decomposition in the solid phase is initiated at nuclei which are situated mainly at the crystal surface, at lattice imperfections, *i.e.*, where a strain exists, these nuclei being regarded in the widest sense as molecules whose decomposition is highly favoured, *i.e.*, of lower activation energy. The mechanism postulated by Prout and Tompkins (*loc. cit.*), which differs somewhat from that of Garner, is briefly as follows: The surface array of product molecules, which in general have a different unit cell from that of the original substance, sets up strains in the crystal surface which are relieved by formation of cracks (not Smekal cracks, which are produced to relieve strain in the *original* crystals, *i.e.*, they are a property of the crystal itself). At the mouths of these cracks, decomposition will be favoured because of lattice imperfections; reaction therefore spreads down these crevices into the crystal. Covering of the surfaces of these cracks now produces lateral strains which ultimately lead to further cracking from the inner surface. Thus a series of "branchings" will occur and planes of strain will be formed, and along these planes the deformation effect of the product on the electronic structure of an adjacent molecule of unreacted substance will be a maximum and decomposition will be favoured. A chain-like reaction develops, which, however, becomes subject to interference since, when a plane of product molecules is encountered, the chain is broken. By a mathematical consideration of their proposed mechanism Prout and Tompkins derived the relationship

$$\log_{10} p / (p_f - p) = k_1 t + c_1$$

where p is the pressure at a time t , p_f the final pressure, and k_1 and c_1 are constants. This equation should hold from the start of appreciable interference with the branching process (*i.e.*, from the early stages of the reaction) to near the inflexion point of the p - t curve, after which the equation

$$\log_{10} p / (p_f - p) = k_2 t + c_2$$

should hold until the end of the reaction is approached. The graph of $\log p / (p_f - p)$ against t should therefore be two straight lines inclined at an angle to each other. The application of these equations to compound (III) is illustrated in Fig. 3, where $\log v / (v_\infty - v)$ has been plotted against t . The values obtained for k_1 and k_2 at various temperatures are given below:

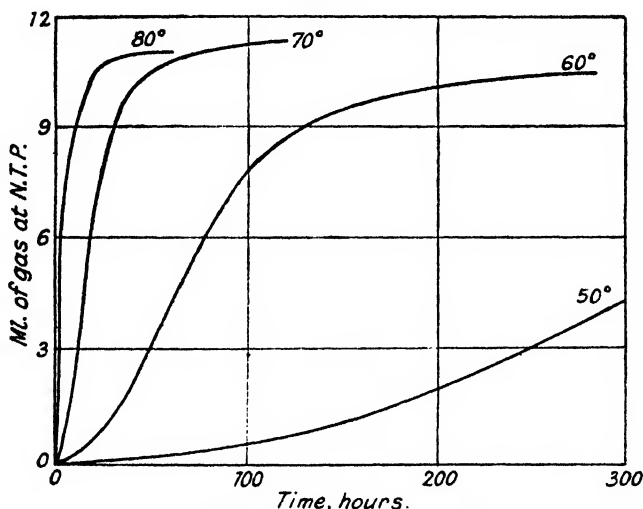
Temp. °	$10^4 k_1$ (sec. ⁻¹), and mean.	$10^4 k_2$ (sec. ⁻¹), and mean.	Temp. °	$10^4 k_1$ (sec. ⁻¹), and mean.	$10^4 k_2$ (sec. ⁻¹), and mean.
90.9°	6.78 } 6.72	8.00 } 8.81	104.4°	38.6 } 39.0	50.1 } 47.7
	6.66 }	8.62 }		39.4 }	45.3 }
95.2	11.0 } 11.3	12.4 } 12.0	110.0	74.5 } 72.6	95.1 } 93.6
	11.6 }	11.6 }		70.6 }	92.1 }
99.1	20.2 } 19.7	22.4 } 21.4			
	19.1 }	20.3 }			

The duplication of values of k_1 is good, but that with k_2 is sometimes not very good, owing probably to the relative inaccuracy of pressure recordings during the final period of reaction. Fig. 4 shows the plot of $\log k_1$ and $\log k_2$ against $1/T$ (where T is the absolute temperature). The slopes of the two lines are almost identical, each giving an activation energy of 35.5 k.-cals. per mol. This indicates that the reactions in both stages are identical, thus supplying further evidence in favour of the theory advanced by Prout and Tompkins. The equations derived by these authors have been used in the interpretation of the volume-time curves obtained from the thermal breakdown of other explosives, and it is hoped to communicate the result of some of this work in the near future.

EXPERIMENTAL.

The method and apparatus used for following the progress of decomposition were essentially those of Farmer (*loc. cit.*). Gas analyses were carried out by a method developed at Bristol University, for details of which we are indebted to Dr. C. E. H. Bawn. This comprises separation of the gases by fractional condensation, followed by analysis of the individual fractions. Fractionation and subsequent analyses were carried out in the absence of air, the gases being pumped off by means of a Toepler pump and measured dry. The main fractions obtained were as follows: Fraction I, gases volatile (in a vacuum) at -186° , comprised O_2 , NO, H_2 , CO, and CH_4 ; Fraction II, gases volatile at -120° , comprised CO_2 and N_2O ; the residue consisted of organic vapours, NO_2 , etc. The individual fractions were analysed by

FIG. 1.



4-Nitrobenzene-2-diazo-1-oxide.

accepted chemical methods. The pure samples of diazo-oxides were prepared and supplied by Dr. T. M. Walters of this Department. They were dried in a vacuum over potassium hydroxide and phosphoric oxide before use. Compounds (I) and (II) were photosensitive and had, therefore, to be dried in the dark. Detailed results obtained were as follows.

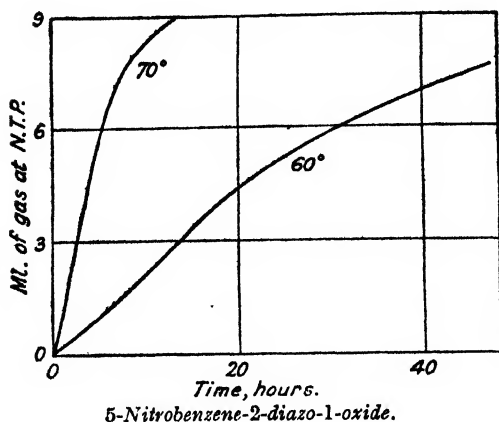
(a) *4-Nitrobenzene-2-diazo-1-oxide* (I).—Thermal decompositions were carried out at 50° , 60° , 70° , and 80° . The gas evolution-time curves were sigmoid in shape (Fig. 1) and decomposition had practically ceased when ca. 0.8 mol. of gas per mol. of (I) had been given off. The gases evolved on complete decomposition at 80° corresponded to 0.84 mol. per mol. of (I) and comprised N_2 , 89.9; NO, 0.7; CO_2 , 8.9; N_2O , 0.5%. It is assumed that the nitrogen is mainly derived from the diazo-group because it is well known that simple aromatic mononitro-compounds are quite stable below ca. 120° . The main reaction involves fission of the diazo-nitrogen, together with a small amount of breakdown of the benzene nucleus. Analysis of the gas at about half-decomposition indicated that the reactions involved are probably the same throughout the decomposition. Decomposition of (I) to which had been added 10% by weight of the reddish-black decomposition residue showed that the end-product is not a catalyst for the reaction and, as would be expected, the volatile products of decomposition were found to be without effect on the characteristics of the breakdown. For decomposition of 0.1 g. at 60° , 70° , and 80° , the times required for evolution of half the final gas volume were approx. 71, 17, and $4\frac{1}{2}$ hrs., respectively. It appears, therefore, that the temperature coefficient of the reaction over this temperature range is 3.5–4 per 10° . Thermal decomposition does not involve complete elimination of diazo-nitrogen; e.g., at 80° only 0.76 mol. (or 1.52 atoms of N) are obtained. The blackish-red colour of the residue and the very intense red colour produced in acetone solution suggest that some coupling had occurred to form a comparatively stable product.

(b) *5-Nitrobenzene-2-diazo-1-oxide* (II).—Typical volume-time curves for thermal breakdown at 60° and 70° are shown in Fig. 2. The rate of thermal decomposition was appreciably greater than that of (I) as is shown by the fact that at 70° the times for evolution of $\frac{1}{2}$ mol. of gas per mol. of (I) or (II) were 20.2 and 6.5 hrs., respectively (0.1 g. tested in each case). The volume-time curve at 60° is sigmoid,

1564 Thermal Decomposition of Explosives in the Solid Phase. Part I.

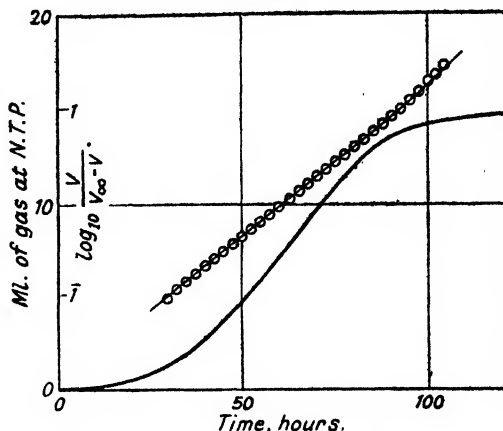
although not as markedly so as with (I), probably owing to the slow decomposition of the latter at this temperature. Complete decomposition at 70° gave 0.77 mol. of gas/mol. of (II), and the composition of

FIG. 2.



5-Nitrobenzene-2-diazo-1-oxide.

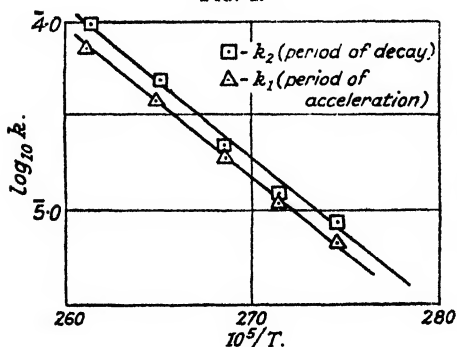
FIG. 3.



2-Nitrobenzene-4-diazo-1-oxide at 99.1°.

this gas was: N_2 , 92.0; CO_2 , 7.1; N_2O , 0.3; NO , 0.6%. After partial decomposition, the composition of the gases evolved was practically the same, indicating that the same main reaction is occurring throughout the decomposition. Of the original diazo-nitrogen only 0.71 mol. (1.42 atoms of N) is eliminated. As with (I), it is probable that some coupling takes place with the formation of a comparatively stable product containing the residual diazo-nitrogen.

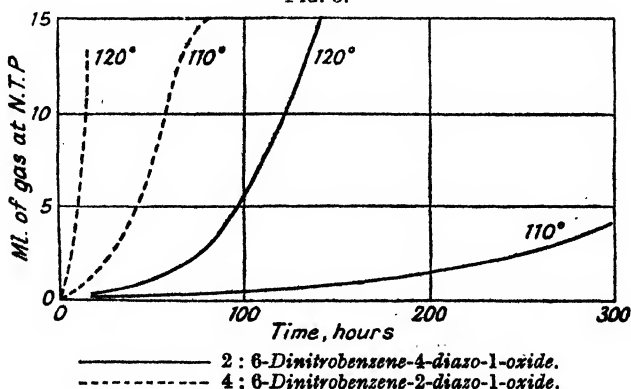
FIG. 4.



(c) 2-Nitrobenzene-4-diazo-1-oxide (III).—Thermal decompositions were conveniently carried out in the range 90—120° and sigmoid volume-time curves were obtained (Fig. 3). On "complete" decomposition at 120°, 1.09 mols. of gas per mol. of (III) were eliminated; the composition of these gases was: N_2 , 90.0; N_2O , 1.0; CO_2 , 7.6; CO , 1.4%, indicating that approximately 0.99 mol. of diazo-nitrogen is eliminated per mol. of (III). From comparison of the time taken to evolve $\frac{1}{2}$ mol. of gas per mol. of (III), a temperature coefficient of 3.5—4 per 10°, for the range 90—110°, was obtained.

(d) 4:6-Dinitrobenzene-2-diazo-1-oxide (IV).—Thermal decompositions were studied in the range 110—120°; typical sigmoid volume-time curves are shown in Fig. 5. The amount of gas evolved on "complete" decomposition is about 1 $\frac{1}{2}$ mol. per mol. of (IV), i.e., far greater than can be accounted for by elimination of the diazo-nitrogen. The composition of the gases was: N_2 , 61.5; NO , 3.0; N_2O , 4.0;

FIG. 5.



CO , 2.5; CO_2 , 28.0%, together with a trace of organic vapours; these results indicate that some breakdown and rearrangement of the benzene nucleus occurs, in addition to loss of diazo-nitrogen.

(e) 2 : 6-Dinitrobenzene-4-diazo-1-oxide (V).—The characteristics of thermal decomposition are similar to those of (IV) and the sigmoid volume-time curves obtained are illustrated in Fig. 5. Compound (V) is, however, considerably more stable than (IV); e.g., 1 mol. of gas is evolved per mol. of (V) in ca. 121 hrs. at 120°, whilst under the same conditions (IV) evolves this amount of gas in 18 hrs. More gas is evolved on "complete" decomposition than can be accounted for by elimination of diazo-nitrogen, and, as with (IV), analysis of this gas indicates that partial breakdown of the benzene nucleus occurs.

The authors wish to express their thanks to the Chief Superintendent, Armament Research, for permission to publish these results.

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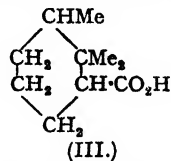
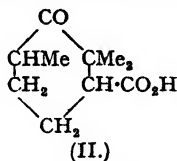
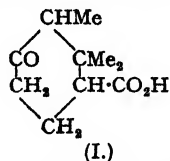
[Received, January 21st, 1947.]

307. Studies in the Terpenes. Part I. A Synthesis of dl-2 : 2 : 3-Trimethylcyclohexane-1-carboxylic Acid.

By R. N. CHAKRAVARTI.

Manasse and Samuel's keto-acid, obtained by the rearrangement of camphorquinone, was previously reduced by the author to a saturated acid, $C_{10}H_{18}O_2$, the structure of which has now been finally settled by a direct synthesis. It has also been found that methyl 2-methylcyclopentan-1-ol-1-carboxylate leads to a mixture of 2 : 2 : 3-trimethyl- and 2 : 2 : 6-trimethylcyclohexanone by pinacolic change.

In their classical researches on the action of concentrated sulphuric acid on camphorquinone, Manasse and Samuel (*Ber.*, 1897, 30, 3157; 1902, 35, 3831) obtained a dextrorotatory acid, $C_{10}H_{18}O_2$, which was found to have the structure (I) or (II). Of these (II) was preferred as the substance failed to give an isonitroso-compound (Gibson and Simonsen, *J.*, 1925, 127, 1295). Later researches on the action of bromine on the keto-acid, however, revealed that it should be represented as *d*-2 : 2 : 3-trimethylcyclohexan-4-one-1-carboxylic acid (I) (Bhagvat and Simonsen, *J.*, 1927, 77; cf. Bredt-Savelsberg, Zaunbrecher, and Knieke, *Ber.*, 1927, 60, 1801).



The *dl*-modification of this acid was prepared in an analogous manner starting from *dl*-camphorquinone (Chakravarti, *J. Indian Chem. Soc.*, 1943, 20, 301). The first clear evidence for the presence of a ketomethylene grouping in the molecule was supplied by the author (*loc. cit.*) when it was found that the corresponding ethyl ester (as I) readily reacted with ethyl oxalate in presence of sodium ethoxide, leading to the formation of an oxalyl derivative. It was also noted that the inactive keto-acid on reduction with amalgamated zinc and concentrated hydrochloric acid gave an acid, $C_{10}H_{18}O_2$ (Chakravarti, *loc. cit.*; see also *Experientia*, 1947, 3, 27), which, on the basis of formula (I) for the keto-acid, should be represented as *dl*-2 : 2 : 3-trimethylcyclohexane-1-carboxylic acid (III). Additional support for the correctness of structure (III) for the reduced acid was afforded by the dehydrogenation of the corresponding methyl ester with selenium to give a mixture of *o*-xylene and *o*-xylene-3-carboxylic acid.

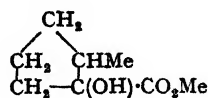
While experiments are in progress for a complete synthesis * of the keto-acid (I), it has now been possible to confirm the structure of the reduced acid as (III) by the following unambiguous synthesis.

Methyl 2-methylcyclopentan-1-ol-1-carboxylate (IV) was allowed to react with excess of methylmagnesium iodide (cf. Meerwein and Unkel, *Annalen*, 376, 152; Chakravarti, *J. Indian*

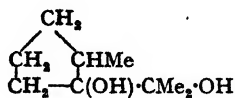
* A partial synthesis of the keto-acid (I) has already been described (Chakravarti, *loc. cit.*). The claim of Guha and Dasgupta (*J. Indian Inst. Sci.*, 1939, 22A, XX, 255) for a complete synthesis of this keto-acid cannot be justified, as the properties of the synthetic acid described by them are wholly inconsistent with those of the *dl*-modification of the acid prepared from *dl*-camphorquinone. The reason is obvious, since, owing to their wrong method of preparation, the product used by them as ethyl α -cyanoglutarate consisted almost wholly (more than 90%) of ethyl γ -cyanopentane- α -cytricarboxylate (cf. Perkin, *J.*, 1904, 85, 417; Ruzicka, Borges de Almeida, and Brack, *Helv. Chim. Acta*, 1934, 17, 183).

For a conversion of santenonequinone into 2 : 3-dimethylcyclohexan-1-one-4-carboxylic acid and a complete synthesis of the latter, see Chakravarti, *J. Indian Chem. Soc.*, 1944, 21, 319, 322.

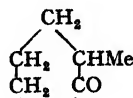
Chem. Soc., 1943, 20, 398) to give the *pinacol* (V). This, on distillation with an aqueous solution of oxalic acid, gave a mixture of the isomeric trimethylcyclohexanones (VI) and (VII) by pinacolic change (cf. Meerwein and Unkel, *loc. cit.*) together with a little non-ketonic product, possibly a mixture of unsaturated hydrocarbons formed by the simple process of dehydration of (V).



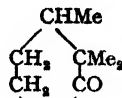
(IV.)



(V.)



(VI.)

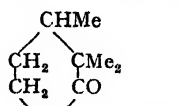


(VII.)

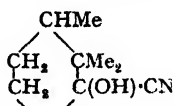
2 : 2 : 3-Trimethylcyclohexanone (VII) had been previously obtained together with 2 : 3 : 6-trimethylcyclohexanone by methylation of 2 : 3-dimethylcyclohexanone with sodamide and methyl iodide (Cornubert and Maurel, *Bull. Soc. chim.*, 1931, 49, 1520). The pure ketone (VII), however, was not obtained, but its presence in the mixture was proved by the isolation of a benzylidene derivative. The inactive modification of the other ketone, 2 : 2 : 6-trimethylcyclohexanone (VI), was isolated from oil of labdanum by Masson (*Compt. rend.*, 1912, 154, 518), who characterised it by the preparation of a semicarbazone, an oxime, and a monobromo-derivative.

In the present instance, the two ketones were separated from the mixture by condensation with ethyl oxalate in presence of sodium ethoxide; according to expectation, only 2 : 2 : 3-trimethylcyclohexanone (VII) furnished an *oxalyl* derivative (VIII). This oxalyl derivative was separated from the neutral matter, and from the latter a semicarbazone was prepared which on hydrolysis with dilute hydrochloric acid gave pure 2 : 2 : 6-trimethylcyclohexanone (VI). This gave an oxime, and in carbon disulphide solution reacted with bromine to give a monobromo-derivative.

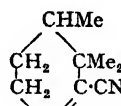
The oxalyl derivative (VIII) on prolonged boiling with concentrated hydrochloric acid gave 2 : 2 : 3-trimethylcyclohexanone (VII) (semicarbazone, benzylidene derivative). (VII) combined almost quantitatively with hydrogen cyanide in presence of a trace of alkali to give a crystalline *cyanohydrin* (IX), which was smoothly dehydrated with excess of phosphorus oxychloride and pyridine to 1-cyano-2 : 2 : 3-trimethylcyclohex-6-ene. This, unlike similar nitriles, was unchanged by prolonged boiling with concentrated hydrochloric acid (cf. Chakravarti, *J. Indian Chem. Soc.*, 1943, 20, 246, 401) or with aqueous or alcoholic potassium hydroxide (cf. Cook and Linstead, *J.*, 1934, 959; King and Robinson, *J.*, 1941, 467), but was hydrolysed by 50% sulphuric acid to 2 : 2 : 3-trimethylcyclohex-6-ene-1-carboxylic acid (XI).



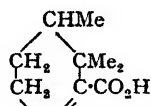
(VIII.)



(IX.)



(X.)



(XI.)

Catalytic hydrogenation of the unsaturated acid (XI) in acetic acid solution in presence of Adams's catalyst gave the desired acid (III) (*p*-phenylphenacyl ester).

EXPERIMENTAL.

2-Methylcyclopentan-1-ol-1-carboxylic acid (as IV) was prepared by the method of Wallach (*Annalen*, 414, 314) with some useful modifications.

The bromination of 2-methylcyclohexanone was carried out under the conditions described by Wallach. After the bromination was complete, however, the acetic acid solution was poured on crushed ice with stirring. The dibromo-ketone separated out as a viscous liquid, which soon solidified. It was filtered off at the pump and washed well with water. The crude product appeared to be rather unstable, as it darkened on keeping, and was always immediately decomposed with alkali in the following way.

The crude dibromo-ketone as obtained from 11.2 g. of 2-methylcyclohexanone was treated with a solution of potassium hydroxide (30 g.) in water (75 c.c.) with shaking, when it readily went into solution with evolution of much heat (some cooling under the tap is necessary as otherwise the product may darken). The solution was gently refluxed on a sand-bath for 45 minutes and then cooled and extracted twice with ether to remove some neutral matter. The alkaline solution was cooled and acidified, when the hydroxy-acid (as IV) separated as a crystalline solid (10.5 g.). The filtrate was saturated with salt and extracted with ether, when a further quantity (about 2 g.) of the acid was obtained. The total yield was directly converted into the methyl ester with methyl alcohol and sulphuric acid. *Methyl*

2-methylcyclopentan-1-ol-1-carboxylate (IV) was obtained as a colourless liquid (12 g.), b. p. 94°/20 mm. (Found : C, 60.4; H, 8.6. $C_8H_{14}O_3$ requires C, 60.7; H, 8.8%).

The Pinacol (V).—A solution of methyl 2-methylcyclopentan-1-ol-1-carboxylate (15.8 g.) in dry ether (25 c.c.) was added dropwise with thorough mixing to an ice-cold solution of methylmagnesium iodide prepared from methyl iodide (26 c.c.) and magnesium (9.6 g.) in ether (75 c.c.). After being kept overnight at the room temperature, the mixture was refluxed on the water-bath for 1½ hours with frequent shaking. The product was well cooled and cautiously decomposed with ice and dilute sulphuric acid. The ethereal layer was separated and the aqueous layer repeatedly extracted with more of the same solvent. The extract was washed with dilute sodium hydroxide solution to remove traces of iodine, and dried (Na_2SO_4). The oily liquid obtained after the removal of ether gave the pinacol (V) as a mobile liquid with a strong camphor-like odour (14 g.), b. p. 110°/19 mm. (Found : C, 68.1; H, 11.5. $C_8H_{16}O_2$ requires C, 68.3; H, 11.4%).

Action of Hot Aqueous Oxalic Acid on the Pinacol (V).—The above product (41 g.) with a 10% aqueous solution of oxalic acid (400 c.c.) was distilled slowly from a flask on a sand-bath. The level of liquid in the flask was kept constant by adding water through a tap funnel as the distillation proceeded. The heating was stopped when there were no more oily drops coming over with the distillate. The total distillate (ca. 500 c.c.) was extracted with ether. The ethereal extract was dried (K_2CO_3) and the solvent was evaporated. The liquid remaining, on distillation, gave a mixture (35 g.), b. p. 170–200°.

This mixture (21 g.) was mixed with ethyl oxalate (22 g.) and added dropwise during 2 hours with shaking to a solution of sodium (3.5 g.) in absolute alcohol (45 c.c.) cooled in a freezing mixture. It was then kept overnight. The product was worked up by adding ice-water and extracting the alkaline solution with ether. From the ethereal solution about 7.5 g. of the neutral unchanged matter (A) were recovered, b. p. 165–190°. The aqueous alkaline solution was acidified with ice-cold dilute sulphuric acid and the separated oil taken up in ether. The extract was washed with water, and then, after evaporation of the solvent, gave the oxalyl derivative (VIII) as an oil (18 g., containing traces of the solvent).

The neutral matter (A) obtained above, after distillation, was heated with semicarbazide acetate in aqueous alcohol. On cooling, the semicarbazone of 2 : 2 : 6-trimethylcyclohexanone separated (3.5 g.). It was obtained pure after two crystallisations from methyl alcohol, m. p. 218° (Masson, *loc. cit.*, gives 220–221°) (Found : C, 61.0; H, 9.6. Calc. for $C_{10}H_{18}ON_3$: C, 60.9; H, 9.6%). The pure semicarbazone on hydrolysis with dilute hydrochloric acid gave pure 2 : 2 : 6-trimethylcyclohexanone (VI) as a volatile liquid with a camphor-like odour, b. p. 180° (Masson, *loc. cit.*, gives b. p. 178–179°) (Found : C, 76.7; H, 11.6. Calc. for $C_8H_{16}O$: C, 77.1; H, 11.4%). It gave an oxime, m. p. 105° (Masson, *loc. cit.*, gives m. p. 106°) (Found : C, 69.6; H, 10.9. Calc. for $C_8H_{17}ON$: C, 69.6; H, 10.9%), and in carbon disulphide solution it reacted with only one mol. of bromine to give a monobromo-derivative, m. p. 41° (Masson, *loc. cit.*, gives m. p. 41°), with evolution of HBr. The monobromo-derivative is very similar to camphor in odour (Found : C, 49.1; H, 6.8; Br, 37.2. Calc. for $C_8H_{15}OBr$: C, 49.3; H, 6.8; Br, 36.5%).

The mother liquor obtained above in the preparation of the semicarbazone gave 3.5 g. of a volatile liquid with a terpene-like smell. This appeared to be a mixture of unsaturated hydrocarbons, but was not further investigated.

Hydrolysis of the Oxalyl Derivative (VIII).—The crude oxalyl derivative obtained above was directly hydrolysed by refluxing it with 20% hydrochloric acid for 48 hours. The liquid was then distilled till the distillate was free from oily drops. The distillate was extracted with ether and the extract dried (K_2CO_3) and fractionated. 2 : 2 : 3-Trimethylcyclohexanone (VII) was obtained as a colourless liquid with camphoraceous odour (9 g.), b. p. 191° (Found : C, 76.8; H, 11.5. $C_8H_{16}O$ requires C, 77.1; H, 11.4%). With semicarbazide acetate in aqueous alcohol it readily gave a semicarbazone crystallising in plates from methyl alcohol, m. p. 214° (mixed m. p. with the semicarbazone of 2 : 2 : 6-trimethylcyclohexanone, 180–185°) (Found : C, 60.9; H, 9.6. $C_{10}H_{18}ON_3$ requires C, 60.9; H, 9.6%). The benzylidene derivative separated from methanol in light yellow needles, m. p. 85° (Found : C, 84.0; H, 8.6. Calc. for $C_{16}H_{20}O$: C, 84.2; H, 8.7%).

1-Cyano-2 : 2 : 3-trimethylcyclohex-6-ene (X).—2 : 2 : 3-Trimethylcyclohexanone (6 g.) was allowed to react with excess of hydrogen cyanide at a low temperature in presence of a drop of potassium cyanide solution. After 10 hours the cyanohydrin was stabilised with a drop of sulphuric acid and the excess of hydrogen cyanide sucked off at the pump, when the product solidified. A small portion of this substance after drying on a porous plate was crystallised from light petroleum, when the pure cyanohydrin (IX) was obtained in colourless needles, m. p. 111°.

The crude cyanohydrin was refluxed for an hour in an oil-bath with excess of phosphorus oxychloride (18 c.c.) and dry pyridine (60 c.c.). It was then cooled and carefully decomposed with ice-water and acidified with hydrochloric acid. By repeated extraction with ether, 1-cyano-2 : 2 : 3-trimethylcyclohex-6-ene (X) was isolated as a colourless liquid (6 g.) with an odour similar to that of phenyl cyanide, b. p. 119°/30 mm. (Found : C, 80.2; H, 9.8. $C_{10}H_{18}N$ requires C, 80.5; H, 10.0%).

2 : 2 : 3-Trimethylcyclohex-6-ene-1-carboxylic Acid (XI).—The unsaturated nitrile obtained above appeared to be particularly resistant to boiling concentrated hydrochloric acid or aqueous or alcoholic potassium hydroxide. It was hydrolysed by gently heating it on a sand-bath for 48 hours with 50% sulphuric acid. In this way a yield of 73% of the unsaturated acid (XI) was obtained. A little neutral matter was also recovered. 2 : 2 : 3-Trimethylcyclohex-6-ene-1-carboxylic acid (XI) crystallised from methyl alcohol in colourless plates, m. p. 135° (Found : C, 71.1; H, 9.4. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.5%).

2 : 2 : 3-Trimethylcyclohexane-1-carboxylic Acid (III).—The unsaturated acid obtained above was hydrogenated in acetic acid solution in presence of Adams' catalyst. The product had b. p. 110°/3 mm. On being kept in the ice-chest it solidified completely. 2 : 2 : 3-Trimethylcyclohexane-1-carboxylic acid (III) crystallised from methanol, at a low temperature, in shining plates, m. p. 58°, undepressed in admixture with the reduced acid (III) as obtained previously (Found : C, 70.5; H, 10.6. Calc. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6%).

The *p*-phenylphenacyl ester of the synthetic acid had m. p. 114°, undepressed in admixture with the *p*-phenylphenacyl ester of the reduced acid (III) (Found: C, 79.1; H, 7.6. Calc. for $C_{24}H_{18}O_2$: C, 79.1; H, 7.7%).

My best thanks are due to Prof. J. C. Bardhan for encouragement and to Mr. J. Chakraverti for facilities.

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[Received, January 23rd, 1947.]

308. *The Preparation and Properties of Triarylstibines.*

By J. I. HARRIS, S. T. BOWDEN, and W. J. JONES.

The influence of nuclear substituents on the reaction of phenylmagnesium halides with antimony trichloride has been examined, and triphenylstibines containing methoxyl, ethoxyl, phenoxyl, chlorine, and bromine as substituents have been prepared. Attempts have also been made to prepare *tri-β-naphthylstibine* through the interaction of *β*-naphthylmagnesium iodide and antimony trichloride. A preliminary examination has been made of the thermal stability of the triphenylstibines.

THE reaction between a substituted phenylmagnesium halide and antimony trichloride has not been studied extensively, and little information is available concerning the influence of nuclear substituents on the properties of triarylstibines. Under ordinary conditions in ethereal solution the reaction between 1 mol. of antimony trichloride and 3 mols. of arylmagnesium halide leads to the formation of the tertiary stibine, $SbAr_3$, and there appears to be no record of the formation of the diarylstibinous chloride, $SbAr_2Cl$, in reactions of this type. In the present investigation, however, it was found that *di-o-anisylstibinous chloride* and *tri-o-anisylstibine* were produced when the antimony halide and *o*-anisylmagnesium bromide reacted in ethereal solution at 40°. It is noteworthy that Makin and Waters (*J.*, 1938, 843) found that triarylstibine dichlorides, $SbAr_3Cl_2$, triarylstibines, and diarylstibinous chlorides were generally produced when diazonium chlorides reacted with antimony under acetone. From bases containing *o*-substituents, only traces of quinquivalent antimony compounds were formed, the main products being the triarylstibines accompanied by a smaller quantity of the diarylstibinous chloride, and it was suggested that the non-formation of quinquivalent antimony compounds may be due to steric hindrance. In the Grignard synthesis, however, there is no possibility of the formation of triarylstibine dichloride, and though the conversion of *di-o-anisylstibinous chloride* into the tertiary stibine may be affected to some extent by steric hindrance, it is evident that this is a subsidiary factor in view of the fact that *o*-phenetylmagnesium bromide reacts with antimony trichloride to give a relatively high yield of *tri-o-phenetylstibine*.

Previous workers have experienced some difficulty in preparing *m*-substituted triphenylstibines by the Grignard synthesis. Thus Challenger and Pritchard (*J.*, 1924, 125, 869) were able to isolate only *tri-m-tolylstibine hydroxychloride* in an attempted preparation of *tri-m-tolylstibine*, and Goddard (*J.*, 1923, 123, 2319) found that the Grignard method gave a low yield of *tri-m-xylylstibine* although the compound may be obtained in high yield by the action of sodium on 4-bromo-*m*-xylene and antimony trichloride. In the present work, it was found that *m*-anisylmagnesium iodide reacted smoothly with antimony trichloride to form *tri-m-anisylstibine* in good yield. The fact that *tri-p-phenoxyphenylstibine* was obtained in fair yield by the Grignard synthesis shows that a phenoxy group does not interfere appreciably with the normal formation of a tertiary stibine.

A chlorine atom in the *p*-position was found to have little effect on the course of the reaction, and the yield of *tri-p-chlorophenylstibine* was good. O'Donnell (*Iowa State Coll. J. Sci.*, 1945, 20, 34) has reported that *tri-p-bromophenylstibine* prepared by the Grignard method is obtained as an oil which can only be converted into crystals, m. p. 134–135°, by inoculation with a specimen of the stibine prepared by reduction of the stibine dichloride, m. p. 184–185°. In the present investigation *tri-p-bromophenylstibine* was obtained as an oil from which a small amount of the crystalline stibine, m. p. 108–109°, was isolated. This material in alcoholic solution gave on treatment with cupric chloride the stibine dichloride, m. p. 200–201°, which agrees with the value given by Makin and Waters (*loc. cit.*), who prepared the dichloride from the diazonium salt and metallic antimony.

The only information given in the literature concerning the thermal stability of triarylstibines is that triphenylstibine undergoes some decomposition when distilled under ordinary pressure (Michaelis and Reese, *Annalen*, 1886, 233, 48) and that *tri-p-diphenylstibine* decom-

poses at the boiling point with formation of antimony, diphenyl, and other products (Worrall, *J. Amer. Chem. Soc.*, 1930, 52, 2048). A survey has therefore been made of the behaviour of triarylstibines at high temperature in nitrogen and in oxygen. When triphenylstibine is kept at 320° in nitrogen for 3 hours it decomposes into benzene, diphenyl (10%), free antimony (17%), and a non-crystallisable antimony compound. The formation of the hydrocarbons arises through the rupture of the Sb-C linkage and the subsequent hydrogenation and dimerisation of the free phenyl radicals to form benzene and diphenyl, respectively. The disproportionation of the radical SbPh_2 , the dimeric form of which has been prepared by Blicke (*J. Amer. Chem. Soc.*, 1931, 53, 1025), is doubtless responsible for the liberation of free antimony and the formation of the complex antimony compound. When triphenylstibine is heated in a sealed tube at 360° for 3 hours, only 9% of the antimony appears in the free state and the amount of diphenyl formed is small. The decomposition is thus facilitated by removal of the more volatile products from the reaction system.

An indication of the thermal stability of a triarylstibine may be obtained by observing the temperature at which the melt becomes turbid when heated in nitrogen. The different influence of *o*-methoxyl and *m*-methoxyl is reflected in the low and the high decomposition temperature, respectively, of tri-*o*- and tri-*m*-anisylstibine as compared with that of triphenylstibine. Tri-*o*-phenetylstibine also has a relatively low decomposition temperature. Nuclear chlorine or bromine does not greatly affect the decomposition temperature but the rate of decomposition is materially reduced. The decomposition temperatures of the triarylstibines in oxygen do not differ appreciably from those in nitrogen, but the rate of reaction is much higher. The behaviour towards oxygen, which is so markedly different from that of the trialkylstibines, shows that the tendency of the antimony atom to increase its 3-covalency is greatly reduced by the presence of aryl groups.

The triarylstibines form dihalides, SbAr_3X_2 , in which the halogen atoms are probably attached to the antimony atom by resonance linkages of the type known to occur in the trialkylstibine dihalides (Wells, *Z. Krist.*, 1938, 99, 367). All the dichlorides and dibromides, except the tri-*o*-phenetyl derivatives, melt without appreciable decomposition. The majority of the alkyloxy- and halogeno-substituted triphenylstibine di-iodides not only melt with decomposition but darken below the melting point.

Tri-o-chlorophenylstibine, tri-*p*-chlorophenylstibine, and tri-*p*-bromophenylstibine are similar to triphenylstibine inasmuch as they do not form a stable addition compound with mercuric chloride at ordinary temperature. It appears that such a compound is formed as an unstable intermediate which undergoes disproportionation into the arylmercuric chloride, HgArCl , and antimony trichloride. The inhibitory influence of alkyloxy- and methyl substituents upon this reaction is much greater than that of halogen substituents.

EXPERIMENTAL.

Tri-o-anisylstibine.—A filtered solution of *o*-anisylmagnesium bromide (1 mol.) was treated with an ethereal solution of antimony trichloride (0.25 mol.). After being boiled for an hour, the mixture was poured into ice-water, and the whole filtered. The residue was extracted first with warm ether (this extract being reserved for later treatment) and then with benzene. The *stibine* was deposited on concentrating the benzene solution; lustrous plates, m. p. 189°, from benzene-chloroform (Found: C, 56.2; H, 5.0; Sb, 27.5. $\text{C}_{11}\text{H}_{11}\text{O}_3\text{Sb}$ requires C, 56.9; H, 4.8; Sb, 27.5%).

Di-o-anisylstibinous Chloride.—The ethereal extract from the above preparation was concentrated, and the deposited *chloride*, after several crystallisations from benzene-alcohol, was obtained in plates, m. p. 116–117° (Found: Cl, 9.3; Sb, 32.4. $\text{C}_{10}\text{H}_{10}\text{O}_2\text{ClSb}$ requires Cl, 9.8; Sb, 32.8%).

Tri-m-anisylstibine.—*m*-Anisylmagnesium iodide was treated with antimony trichloride as described above. After treatment with ice-water, the ethereal solution was evaporated and the residual oil was subjected to steam-distillation to remove volatile material. From an alcoholic solution of the oil, the *stibine* separated in plates; yield 50%. The pure *stibine* had m. p. 88.5–89.0° (Found: C, 56.8; H, 5.0; Sb, 27.2. $\text{C}_{11}\text{H}_{11}\text{O}_3\text{Sb}$ requires C, 56.9; H, 4.8; Sb, 27.5%).

Tri-o-phenetylstibine.—Prepared from *o*-phenetylmagnesium bromide and antimony trichloride, the *stibine* was obtained in 56% yield; needles, m. p. 123.5–123.8°, from alcohol (Found: C, 59.7; H, 5.6; Sb, 25.2. $\text{C}_{14}\text{H}_{17}\text{O}_3\text{Sb}$ requires C, 59.4; H, 5.6; Sb, 25.1%).

Tri-p-phenoxyphenylstibine.—*p*-Phenoxyphenylmagnesium bromide was prepared by refluxing for 24 hours *p*-bromodiphenyl ether, ether, and magnesium powder which had been activated *in situ* by strong heating with iodine. To favour completion of the reaction, benzene was added in the latter stages. The filtered solution was treated with antimony trichloride as previously described. The *stibine* was obtained as a white solid, m. p. 157°, after repeated crystallisation from alcohol (Found: C, 69.1; H, 4.5; Sb, 19.4. $\text{C}_{18}\text{H}_{19}\text{O}_3\text{Sb}$ requires C, 68.7; H, 4.3; Sb, 19.4%).

Tri-o-chlorophenylstibine.—The *stibine* was prepared from *o*-chlorophenylmagnesium bromide and antimony trichloride, but the yield was very low. After repeated crystallisation from glacial acetic acid and then from alcohol-benzene, the compound was obtained in white feathery crystals, m. p. 136–137° (Found: Cl, 23.1; Sb, 26.4. $\text{C}_{10}\text{H}_9\text{Cl}_2\text{Sb}$ requires Cl, 23.3; Sb, 26.7%). The *stibine* did not reduce

cupric chloride in alcoholic solution at room temperature, but it reacted with bromine and iodine. The stibine did not form a stable mercurichloride.

Tri-*p*-chlorophenylstibine.—No appreciable amount of dimagnesium derivative was produced in the reaction of *p*-chlorobromobenzene with magnesium (cf. Bodroux, *Compt. rend.*, 1903, 136, 1138). Treatment of *p*-chlorophenylmagnesium bromide with antimony trichloride gave the stibine; feathery crystals, m. p. 99.5–100.5°, from alcohol–benzene (Found: C, 47.3; H, 2.5; Cl, 23.5; Sb, 26.9. $C_{18}H_{15}Cl_3Sb$ requires C, 47.4; H, 2.7; Cl, 23.3; Sb, 26.7%).

Tri-*p*-bromophenylstibine.—Interaction of *p*-bromophenylmagnesium bromide and antimony trichloride gave a low yield of the stibine; glistening crystals, m. p. 109.8–110.4°, from alcohol–benzene (Found: Br, 40.5; Sb, 20.4. Calc. for $C_{18}H_{15}Br_3Sb$: Br, 40.6; Sb, 20.6%). The pure stibine was very soluble in benzene, ether, and chloroform, but only slightly soluble in light petroleum. It reacted with mercuric chloride in alcoholic solution to form a white precipitate which could not be recrystallised from the usual solvents.

Tri- β -naphthylstibine.— β -Iodonaphthalene (Schmidlin and Huber, *Ber.*, 1910, 43, 2829) was converted into the magnesium derivative, which was treated with antimony trichloride in accordance with the usual procedure. After the solution had been boiled for an hour and then treated with ice-water, the mixture was filtered. The solid was repeatedly extracted with hot benzene, and after removal of the solvent, the residual oil was triturated with ligroin until it solidified. Repeated crystallisation of the material from acetone gave the stibine as a yellow solid which partly melted at 195° (Found: C, 69.3; H, 4.9; Sb, 23.3. $C_{30}H_{21}Sb$ requires C, 71.6; H, 4.2; Sb, 24.2%). The yield was very low and the stibine could not be further purified owing to its slight solubility in the usual organic solvents. It did not form an addition compound with mercuric chloride and did not reduce cupric chloride, but it reacted with light petroleum solutions of bromine and iodine.

Addition Compounds.—The addition compounds listed in the table were prepared by treating the triarylstibine with solutions of cupric chloride, bromine, iodine, or mercuric chloride. Inasmuch as the majority of the di-iodides are susceptible to hydrolysis by traces of moisture, all reagents used in their preparation were thoroughly dried before use.

Stibine dichlorides, Ar_3SbCl_2 .

Ar.	Cryst. form and solvent.*	M. p.	Found, %.		Formula.	Required, %.	
			Cl.	Sb.		Cl.	Sb.
<i>o</i> -Anisyl	White crystals; A	237–238°	14.2	23.4	$C_6H_4O_2Cl_2Sb$	13.8	23.7
<i>m</i> -Anisyl	As above	81.5–82.5	14.2	23.6	$C_6H_4O_2Cl_2Sb$	13.8	23.7
<i>o</i> -Phenetyl	Colourless crystals; B	231–232 †	13.0	22.1	$C_6H_4O_2Cl_2Sb$	12.8	21.9
<i>p</i> -Phenoxyphenyl ..	Needles; B	106–107	10.3	16.9	$C_8H_7O_2Cl_2Sb$	10.1	17.4
<i>p</i> -Chlorophenyl ...	Needles; C	193.0–193.5	13.5 †	23.1	$C_6H_4Cl_2Sb$	13.5 †	23.1
<i>p</i> -Bromophenyl ...	Needles; B	200–201	10.6	18.3	$C_6H_4Br_2Cl_2Sb$	10.7	18.4

Stibine dibromides, Ar_3SbBr_2 .

		M. p.	Br.			Br.	
			Br.	Sb.		Br.	Sb.
<i>o</i> -Anisyl	Glistening crystals; A	225–226	26.8	20.5	$C_6H_4O_2Br_2Sb$	26.5	20.2
<i>m</i> -Anisyl	Pale yellow needles; B	74.5–75.5	26.9	20.0	$C_6H_4O_2Br_2Sb$	26.5	20.2
<i>o</i> -Phenetyl	As above	237–238 †	24.9	18.8	$C_6H_4O_2Br_2Sb$	24.8	18.9
<i>p</i> -Phenoxyphenyl ..	White needles; B	151–152	20.4	15.0	$C_8H_7O_2Br_2Sb$	20.3	15.4
<i>p</i> -Chlorophenyl ...	Lustrous plates; D	189.5–190.0	26.3	20.0	$C_6H_4Cl_2Br_2Sb$	25.9	19.8
<i>p</i> -Bromophenyl ...	Needles; B	182	21.5 †	16.4	$C_6H_4Br_2Sb$	21.3 †	16.3

Stibine di-iodides, Ar_3SbI_2 .

		M. p.	I.			I.	
			I.	Sb.		I.	Sb.
<i>o</i> -Anisyl	Yellow solid; D	141–142 †	30.7	17.3	$C_6H_4O_2I_2Sb$	36.4	17.5
<i>m</i> -Anisyl	Pale yellow plates; B	99.5–100.0	30.2	17.6	$C_6H_4O_2I_2Sb$	36.4	17.5
<i>o</i> -Phenetyl	As above	143 †	34.6	16.6	$C_6H_4O_2I_2Sb$	34.3	16.5
<i>p</i> -Phenoxyphenyl ..	As above	140 †	28.5	14.1	$C_8H_7O_2I_2Sb$	28.7	13.8
<i>p</i> -Chlorophenyl ...	Yellow plates; E	137–138 †	36.2	17.2	$C_6H_4Cl_2I_2Sb$	35.7	17.2
<i>p</i> -Bromophenyl ...	Pale yellow needles; C	155–156 †	29.9	14.6	$C_6H_4Br_2I_2Sb$	30.1	14.4

Mercurichlorides, $Ar_3SbHgCl_2$.

		M. p.	Cl.			Cl.	
			Cl.	Sb.		Cl.	Sb.
<i>o</i> -Anisyl	White solid; B	160–161	10.4	28.5 ‡	$C_6H_4O_2SbHgCl_2$	9.9	28.1 §
<i>m</i> -Anisyl	As above	180 †	10.2	16.9	$C_6H_4O_2SbHgCl_2$	9.9	17.0
<i>o</i> -Phenetyl	As above	170.9	9.7	16.1	$C_6H_4O_2SbHgCl_2$	9.4	16.1
<i>p</i> -Phenoxyphenyl ..	White crystals; F	175–176 †	—	13.3	$C_8H_7O_2SbHgCl_2$	—	13.5

* A = $CHCl_3$ –light petroleum; B = alcohol–chloroform; C = light petroleum; D = carbon tetrachloride–light petroleum; E = alcohol–light petroleum; F = benzene–alcohol.

† With decomposition.

‡ Values relate to hydrolysable halogen.

§ Hg, not Sb.

Thermal Stability of Triarylstibines.—The temperature of the stibine was raised at a rate of 3–4°/min. by heating the material in a stream of nitrogen or oxygen in a small vessel provided with a side-tube in communication with U-tubes for the condensation of volatile products. The temperature at which turbidity first appeared in the molten stibine was taken as the decomposition temperature; those in nitrogen and oxygen, respectively, were as follows: triphenylstibine, 250°, 265°; tri-*o*-anisylstibine, 200°, 200°; tri-*m*-anisylstibine, 258°, 260°; tri-*o*-phenetylstibine, 200°, 205°; tri-*o*-chlorophenylstibine, 260°, —; tri-*p*-chlorophenylstibine, 230°, 265°; tri-*p*-bromophenylstibine, 262°, 250°; tri-*p*-phenoxyphenylstibine, 265°, 260°. Although there was generally little difference between the decomposition temperatures in nitrogen and in oxygen, the rate of reaction was invariably higher in the latter.

Triphenylstibine (1 g.), maintained at 325° for 3 hours under nitrogen in the above apparatus, gave a

small amount of benzene, and diphenyl (0.1 g.). The grey residue in the pyrolysis vessel consisted of a viscous oil and a finely-divided solid. After being washed with acetone, the solid (0.17 g.) was shown to be free antimony (Found : Sb, 99.4%). The acetone solution of the oil gave a positive test for antimony, but no solid product could be isolated.

Triphenylstibine (10 g.) was maintained at 360° in a sealed tube for 3 hours. On cooling, the tube was found to be free from excess pressure, and the pyrolysis product consisted of free antimony (0.3 g. Found : Sb, 99.3%) and a pale green viscous liquid. The latter on fractionation gave triphenylstibine (8.4 g.) and a residue which could not be crystallised. In a repetition of the experiment, the pyrolysis product was subjected to steam-distillation, but the amount of diphenyl isolated was small.

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[Received, January 24th, 1947.]

309. *The Synthesis of α -Amino- γ -(*p*-hydroxyphenyl)butyric Acid, a Homologue of Tyrosine.*

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Because of the known intermediate formation of indole derivatives in the *in vitro* production of melanin from tyrosine under the influence of tyrosinase, it became of interest to study the action of this enzyme on the next higher homologue of tyrosine. By this means it seemed possible that data relating to the analogous formation of quinoline compounds by enzyme action might be obtained.

α -Amino- γ -(*p*-hydroxyphenyl)butyric acid has been synthesised by two different routes, and some related intermediate compounds are described.

THE elucidation of the series of chemical reactions involved in the formation of melanin from tyrosine under the influence of the enzyme tyrosinase has been the subject of several investigations (see Raper *et al.*, *Physiol. Rev.*, 1928, 8, 245; Evans and Raper, *Biochem. J.*, 1937, 31, 2162; Clemo and Weiss, *J.*, 1945, 702). In the presence of tyrosinase, a number of compounds structurally related to tyrosine, and possessing great physiological interest (*e.g.*, adrenaline, epinine, tyramine, etc.) are oxidised and give rise, where the side-chain configuration allows, to indole compounds, the formation of which has been established in most cases (Dulière and Raper, *Biochem. J.*, 1930, 24, 259). It is generally assumed that the *o*-quinone of 3 : 4-dihydroxyphenylalanine undergoes ring closure spontaneously, without mediation of the enzyme. With esters of tyrosine, however, and compounds where the amino-group is fully alkylated, including quaternary ammonium salts, ring closure does not take place after quinone formation, although additional oxygen is utilised, the subsequent course of the reaction being unknown. It is clear from the work of Bloch and Schaaf (*Biochem. Z.*, 1926, 162, 181) and of Heard and Raper (*Biochem. J.*, 1933, 27, 36) that under changed conditions of pH and temperature, side reactions occur to a greater or less extent, a fact which the latter authors deem important in relation to the biochemical origin of adrenaline from tyrosine or some similar precursor.

α -Amino- γ -(*p*-hydroxyphenyl)butyric acid has been synthesised in order to study the action of tyrosinase on it, with particular reference to the fate of the side chain. If the reaction follows an analogous course to the tyrosine-tyrosinase system, the eventual formation of quinoline derivatives would be expected.

Attempts to effect the condensation of *p*-methoxyphenylacetaldehyde with hippuric acid, acetylglycine, or hydantoin failed to yield the anticipated derivatives of α -amino- γ -(*p*-methoxyphenyl)butyric acid, in spite of a large variety of experimental conditions.

Two alternative methods for the synthesis of α -amino- γ -(*p*-hydroxyphenyl)butyric acid were employed : (a) β -(*p*-Methoxyphenyl)propionitrile, prepared from anisaldehyde, was reduced by stannous chloride under the usual conditions of the Stephen reaction to yield *p*-methoxyphenylpropaldehyde, which, when condensed with ammonium cyanide, followed by hydrolysis of the resulting aminocyanohydrin, afforded α -amino- γ -(*p*-methoxyphenyl)butyric acid. The latter compound was demethylated by treatment with hydriodic acid and red phosphorus in the usual manner to yield the desired amino-acid.

(b) 2-(*p*-Aminophenyl)ethyl bromide, obtained by reducing the corresponding nitro-compound, was converted into 2-(*p*-hydroxyphenyl)ethyl bromide by diazotisation of the amino-group followed by hydrolysis of the diazonium compound in the usual manner. The hydroxy-compound was condensed with the sodio-derivative of benzamidomalonic ester in anhydrous ethanol (*cf.* Redemann and Dunn, *J. Biol. Chem.*, 1939, 130, 341), and hydrolysis of the condensation product with aqueous hydrobromic acid gave the desired α -amino- γ -(*p*-hydroxyphenyl)butyric acid. The results of the investigation on the action of tyrosinase on this amino-acid will be reported later.

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EXPERIMENTAL.

(All m. ps. are uncorrected.)

p-Methoxyphenylpropionitrile (cf. Goldschmidt and Fraenkel, *Monatsh.*, 1914, **35**, 283).—*p*-Methoxyphenylpropionamide (6 g.), obtained by the method of Barger and Walpole (*J.*, 1909, **95**, 1724), dissolved in dry xylene, was boiled vigorously whilst phosphoric oxide (12 g.) was added in small portions with shaking. The mixture was boiled under reflux for 15 minutes, the reaction liquid filtered, and the xylene removed by distillation under reduced pressure on the water-bath. The residue was distilled under reduced pressure, and the fraction, b. p. 160–165/13 mm. (3 g., yield 50%), was collected. It was a colourless oil possessing a characteristic smell.

p-Methoxyphenylpropaldehyde.—Finely powdered anhydrous stannous chloride (10 g., 1.5 mols.) was suspended in dry ether (25 c.c.), cooled in ice and saturated with dry hydrogen chloride, until a homogeneous solution was obtained. *p*-Methoxyphenylpropionitrile (5 g., 1 mol.) was then added, the reaction mixture shaken vigorously, and the stoppered reaction vessel set aside at room temperature overnight. The white, crystalline aldimino-stannichloride which separated was collected on a dry filter, and washed with dry ether. It was hydrolysed to the aldehyde by suspension in warm water made definitely alkaline with aqueous sodium carbonate, followed by extraction with ether. The ethereal solution was dried (Na_2SO_4), and the solvent removed. The oily residue was distilled under reduced pressure, giving *p*-methoxyphenylpropaldehyde, b. p. 130–135°/15 mm. (4.8 g., 90%). On condensation with semicarbazide hydrochloride in the usual way, it gave a *semicarbazone*, which on crystallisation from benzene afforded white needles, m. p. 140–142° (Found: C, 59.2; H, 7.0; N, 18.7. $\text{C}_{11}\text{H}_{11}\text{O}_2\text{N}_2$ requires C, 59.1; H, 6.8; N, 19.0%). This aldehyde could also be obtained, in poor yield, by distillation under reduced pressure of an intimate mixture of the barium salt of *p*-methoxyphenylpropionic acid with barium formate and silver sand.

*α -Amino- γ -(*p*-methoxyphenyl)butyric Acid.*—A modification of Strecker's synthesis due to Lapworth and Cocker (*J.*, 1931, 1371) was employed. *p*-Methoxyphenylpropaldehyde (4.5 g., 1 mol.) was added gradually, with stirring, to a well-cooled solution of ammonia (0.9 g., *d* 0.88, 2 mols.) and hydrogen cyanide (1.4 g., 2 mols.). The reaction mixture was shaken mechanically at room temperature for several hours, and left for 2 days to attain equilibrium. To the mixture, which had now darkened appreciably, was slowly added excess of sulphuric acid (40% w/v; 5–7 mols.). Hydrolysis was effected by heating for 3 hours at 125° until a test portion of the solution gave no reaction for ferrocyanide with excess of sodium hydroxide and ferrous hydroxide. The solution was diluted with several times its volume of water, and powdered barium carbonate (A.R.) was gradually added until the mixture was definitely alkaline to litmus. Steam was passed through the boiling solution until all the ammonia had been driven off. The bulky precipitate of barium sulphate was filtered off, and well washed with boiling, very dilute aqueous sulphuric acid. The combined filtrates were treated with powdered lead carbonate until effervescence ceased, and the solution no longer showed an acid reaction to Congo-red, the mixture filtered, and the residue of lead sulphate washed with water. The combined filtrate and washings were saturated with hydrogen sulphide, the lead sulphide removed, and the filtrate concentrated to a small bulk (50 c.c.). The concentrate was decolorised (norite) and filtered, and on further concentration and cooling, a white crystalline solid separated. After recrystallisation from aqueous alcohol the *amino-acid* formed needles (2 g., 35%), m. p. 245–246° (Found, C, 63.1; H, 6.9; N, 6.75. $\text{C}_{11}\text{H}_{11}\text{O}_3\text{N}$ requires C, 63.2; H, 7.1; N, 6.7%).

*α -Amino- γ -(*p*-hydroxyphenyl)butyric Acid.*—The above methoxy-acid was demethylated by the method of Harington and McCartney (*Biochem. J.*, 1927, **21**, 852), the acid (5 g.), red phosphorus (5 g.), hydriodic acid (25 c.c., *d* 1.7), and acetic anhydride (25 c.c.) being boiled together under reflux for 1.5 hours. The reaction mixture was filtered through asbestos-wool, the phosphorus well washed with glacial acetic acid, and the filtrate evaporated to dryness in a vacuum. Water was then added, and the evaporation repeated. The residue was taken up in a little water, and sufficient lead carbonate added just to neutralise the trace of acid present and to remove the iodine. The precipitate was filtered off and washed thoroughly with distilled water, the filtrate saturated with hydrogen sulphide, the lead sulphide removed, and the clear filtrate decolorised (norite) and concentrated to small bulk. On cooling, crystals soon developed, which were collected and recrystallised twice from boiling water, whence a white micro-crystalline powder was obtained (1.5 g.) m. p. 265° (Found, C, 61.5; H, 6.7; N, 7.2. $\text{C}_{10}\text{H}_9\text{O}_3\text{N}$ requires, C, 61.5; H, 6.66; N, 7.18%). The *amino-acid* on treatment with a solution of diazotised *o*-chloroaniline gave a red azo-compound. Nitrogen was evolved on treatment with cold nitrous acid.

p-(2-Bromoethyl)aniline Hydrochloride.—2-(*p*-Nitrophenyl)ethyl bromide (10 g.), prepared from 2-phenylethyl alcohol by the method of Foreman and McElvain (*J. Amer. Chem. Soc.*, 1940, **62**, 1436), was added in 1 g. portions to a solution of stannous chloride (40 g.) in concentrated hydrochloric acid (100 c.c.) which was heated on the steam-bath, the liquid being shaken vigorously after each addition; the solid nitro-compound melted to an oil, which gradually reacted, and dissolved on shaking, a further portion being then added. When the addition was completed, the mixture was heated on the steam-bath for a further 45 minutes. The reaction mixture was then freed from a little oil by extraction with hot benzene, and the aqueous layer was separated, and cooled in a freezing mixture. An excess of aqueous sodium hydroxide was added, with careful cooling until all the tin, which was at first precipitated as hydroxide, had dissolved. The alkaline solution was thrice extracted with ether, the combined extract washed with water, and the amine was removed from the ether by shaking with 3.5*N*-hydrochloric acid (22 c.c.). After separation of the aqueous layer, *p*-(2-bromoethyl)aniline hydrochloride (7.75 g.) crystallised out; it recrystallised from water in nearly colourless needles, m. p. 211° (decomp.).

p-(2-Bromoethyl)phenol.—The foregoing hydrochloride (10 g.) was dissolved in water (100 c.c.) and 30% sulphuric acid (20 c.c.), the mixture warmed to 55°, and a solution of sodium nitrite (3.5 g.) in water (20 c.c.) was added slowly, with mechanical stirring. A dark reddish-brown oil possessing a sharp sickly smell separated, and the mixture was heated on the steam-bath for a further 15 minutes, then cooled;

the oil was extracted with ether, the extract dried (Na_2SO_4), the solvent removed, and the residual oil distilled, yielding *p*-(2-bromethyl)phenol (2.3 g.) as a viscous yellow oil, b. p. 150–155°/12 mm.

*α -Amino- γ -(*p*-hydroxyphenyl)butyric Acid*.—Benzamidomalonate ester (2.8 g.), prepared as described by Redemann and Dunn (*J. Biol. Chem.*, 1939, 130, 341) but with Painter's modification (*J. Amer. Chem. Soc.*, 1940, 62, 232), was added to a hot solution of sodium (0.25 g.) in absolute alcohol (50 c.c.), and when the solid sodio-derivatives had separated *p*-(2-bromoethyl)phenol (2.3 g.) was added, and the mixture heated under reflux for 3 hours. The bulk of the alcohol was removed by distillation, and the residue diluted with water (100 c.c.) and extracted with ether. The extract was dried (Na_2SO_4), and the solvent removed, leaving ethyl 2-(*p*-hydroxyphenyl)ethylbenzamidomalonate as a brown oil (3 g.). This was hydrolysed by refluxing with 48% aqueous hydrobromic acid (20 c.c.) for 10 hours. The mixture was diluted with boiling water (40 c.c.), filtered, and left in the ice-chest overnight. Benzoic acid separated, and was filtered off, the filtrate being evaporated to dryness in a vacuum. The residual solid was extracted with water (15 c.c.), the extract boiled (norite), filtered, and the filtrate carefully neutralised with aqueous ammonia and kept in the ice chest for 24 hours. *α -Amino- γ -(*p*-hydroxyphenyl)butyric acid* (0.17 g.), m. p. 265° (decomp.), separated as a microcrystalline powder; recrystallised from 50% aqueous alcohol, it had m. p. 265° (decomp.) undepressed on admixture with the amino-acid synthesised by the previous route (Found: C, 60.3; H, 6.52; N, 7.2%).

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[Received, January 30th, 1947.]

310. Some 1:1'- and 2:2'-Dinaphthyl Derivatives and a New Synthesis of 3:3'-Dinitro-1:1'-dinaphthyl.

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3:3'-Dinitro-1:1'-dinaphthyl, formerly prepared by the action of copper on 1-iodo-3-nitronaphthalene, is now synthesised from naphthidine.

4:4'-DIACETAMIDO-1:1'-DINAPHTHYL readily dinitrated to give 3:3'-dinitro-4:4'-diacetamido-1:1'-dinaphthyl which was hydrolysed by boiling ethyl-alcoholic sulphuric acid to 3:3'-dinitro-4:4'-diamino-1:1'-dinaphthyl, a compound easily bisdiazotised by a nitrosyl-glacial acetic acid procedure (cf. Hodgson and Walker, *J.*, 1933, 1620; Schoutissen, *J. Amer. Chem. Soc.*, 1933, 55, 4535). Replacement of both diazo-groups by hydrogen was effected by means of ethanol to give 3:3'-dinitro-1:1'-dinaphthyl in over 80% yield, a compound previously prepared in poor yield by the action of copper on 1-iodo-3-nitronaphthalene (cf. Cumming and Howie, *J.*, 1931, 3179; Chudožilov, *Chem. Listy*, 1925, 19, 187). Reduction to 3:3'-diamino-1:1'-dinaphthyl by the procedure of Cumming and Howie (*loc. cit.*) was confirmed, and so the 3:3'-positions taken up by the nitro-groups in the original nitration of 4:4'-diacetamido-1:1'-dinaphthyl were established. Replacement of the amino- by hydroxyl groups in 3:3'-dinitro-3:3'-diamino- or 3:3'-diacetamido-1:1'-dinaphthyl to give 3:3'-dinitro-4:4'-dihydroxy-1:1'-dinaphthyl was effected by boiling aqueous sodium hydroxide, and the disodium salt of this compound was sparingly soluble in cold water.

1:1'-DIACETAMIDO-2:2'-DINAPHTHYL is dinitrated in the 4:4'-positions to give 4:4'-dinitro-1:1'-diacetamido-2:2'-dinaphthyl, as proved by hydrolysis with ethanol and concentrated sulphuric acid to give the known 3:6-dinitro-1:2:7:8-dibenzocarbazole (Hodgson and Habeshaw, this vol., p. 77).

EXPERIMENTAL.

Nitration of 4:4'-Diacetamido-1:1'-dinaphthyl.—The diacetyl compound (1.9 g.), prepared by the addition of acetic anhydride to a boiling solution of naphthidine in glacial acetic acid (cf. Cumming and Howie, *J.*, 1932, 528), was added gradually in a finely divided state with stirring to nitric acid (35 c.c., *d* 1.42), the temperature being maintained below 15°; the solution darkened as the solid dissolved and, after about 15 minutes, a yellow precipitate of 3:3'-dinitro-4:4'-diacetamido-1:1'-dinaphthyl began to separate. After being stirred for 30 minutes from the final addition of the acetyl compound, the mixture was poured into water, the yellow precipitate (1.95 g., m. p. 332–335°) filtered off, washed acid free with water, dried, and crystallised first from nitrobenzene in which it was moderately soluble and then from glacial acetic acid in which it was sparingly soluble, to give yellow micro-crystals, m. p. 342–343° (Found: N, 12.5. $\text{C}_{20}\text{H}_{14}\text{O}_4\text{N}_4$ requires N, 12.2%).

3:3'-Dinitro-4:4'-diamino-1:1'-dinaphthyl.—This was obtained by refluxing the diacetyl derivative above (5 g.) for 10 hours with ethanol (50 c.c.) and dilute sulphuric acid (50 c.c., *d* 1.08); the solution deepened in colour and on being poured into water (600 c.c.) afforded the free amine (4.5 g.) which was filtered off, washed with water until acid-free and then with ethyl acetate, and crystallised once from nitrobenzene in which it was readily soluble at the boil and twice from glacial acetic acid in which it was moderately soluble, to give bright yellow micro-plates, m. p. 338–339° (Found: N, 14.8. $\text{C}_{20}\text{H}_{14}\text{O}_2\text{N}_4$ requires N, 15.0%).

3:3'-Dinitro-1:1'-dinaphthyl.—This was prepared by addition of finely powdered 3:3'-dinitro-

4 : 4'-diamino-1 : 1'-dinaphthyl (5.7 g.) to a mixture of sodium nitrite (7 g.) in sulphuric acid (60 c.c., *d* 1.84) below 40°; a deep green solution was formed which was diluted with glacial acetic acid at such a rate that the temperature was kept between 45° and 50°, and the colour became golden-brown. After being stirred for 1 hour, the mixture was added gradually to ethanol (200 c.c.) and, when the reaction had moderated, the whole was heated on the water-bath under the reflux for 1 hour, after which the volatile portion was removed by distillation until the residual volume was ca. 100 c.c.; it was then poured into water (500 c.c.). The light brown precipitate of 3 : 3'-dinitro-1 : 1'-dinaphthyl (4.6 g.) was filtered off, washed acid free with water, crystallised once from nitrobenzene and twice from glacial acetic acid, and so obtained in golden yellow plates, m. p. 280—281° (Cumming and Howie, *loc. cit.*, give m. p. 281°; Chudožilov, *loc. cit.*, gives m. p. 262—264°) (Found : N, 8.3. Calc. for $C_{20}H_{14}O_4N_2$: N, 8.1%). This compound (2.4 g.), when boiled for 5 hours with glacial acetic acid (180 c.c.) and zinc dust (20 g.) during the gradual addition of hydrochloric acid (2 c.c., *d* 1.18), was reduced to 3 : 3'-diamino-1 : 1'-dinaphthyl which was removed from the cold reaction mixture, after it had been made alkaline with solid sodium hydroxide, by ether extraction; after removal of the ether from the dried extract, the residue of the crude 3 : 3'-diamino-1 : 1'-dinaphthyl crystallised from benzene in white plates, m. p. 269—270° (Cumming and Howie, *loc. cit.*, give m. p. 270°) (Found : N, 10.1. Calc. for $C_{20}H_{16}N_2$: N, 9.9%).

3 : 3'-Dinitro-4 : 4'-dihydroxy-1 : 1'-dinaphthyl.—This was formed when 3 : 3'-dinitro-4 : 4'-diamino-1 : 1'-dinaphthyl (2 g.) was refluxed with 20% aqueous sodium hydroxide (50 c.c.) for 2 hours; when the red disodium salt of the dihydroxy-compound began to be deposited, the mixture was filtered hot, and, on cooling, an almost quantitative yield was obtained in reddish-brown crystals (Found : Na, 10.8. $C_{20}H_{10}O_6N_2Na_2$ requires Na, 11.0%), which were sparingly soluble in cold but readily so in hot water. When the sodium salt was mixed with dilute acids, 3 : 3'-dinitro-4 : 4'-dihydroxy-1 : 1'-dinaphthyl was liberated and crystallised from glacial acetic acid in which it was moderately soluble in yellow micro-plates, m. p. 319—320° (Found : N, 7.6. $C_{20}H_{14}O_6N_2$ requires N, 7.4%).

3 : 3'-Diamino-4 : 4'-diacetamido-1 : 1'-dinaphthyl.—This was obtained when a solution of 3 : 3'-dinitro-4 : 4'-diacetamido-1 : 1'-dinaphthyl (2 g.) in boiling glacial acetic acid (150 c.c.) was treated gradually with zinc dust (20 g.) during 45 minutes, the mixture refluxed a further 30 minutes, and filtered hot into water (500 c.c.). The flocculent precipitate was extracted with boiling water (100 c.c.) containing hydrochloric acid (50 c.c., *d* 1.18) and the filtered extract cooled; the dihydrochloride of 3 : 3'-diamino-4 : 4'-diacetamido-1 : 1'-dinaphthyl then separated (1.2 g.) in white feathery needles which did not melt (Found : ionic chlorine, 14.9. $C_{24}H_{22}O_2N_4 \cdot 2HCl$ requires Cl, 15.1%), and were only sparingly soluble in cold water but readily so in hot water and dilute acids. After basification with dilute ammonia, the white precipitate of 3 : 3'-diamino-4 : 4'-diacetamido-1 : 1'-dinaphthyl was crystallised from glacial acetic acid, giving white micro-crystals which carbonised at 390° (Found : N, 13.9. $C_{24}H_{22}O_2N_4$ requires N, 14.1%), and were almost insoluble in benzene, xylene, or ethanol.

1 : 1'-Diacetamido-2 : 2'-dinaphthyl.—This was prepared by stirring a suspension of 1 : 1'-diamino-2 : 2'-dinaphthyl (1.7 g.) in acetic anhydride (25 c.c.) for 24 hours at room temperature (cf. Cumming and Howie, *J.*, 1932, 531); attempts to make this compound more rapidly by hot acetylation resulted in the formation of 1 : 2 : 7 : 8-dibenzocarbazole, which crystallised from benzene in white needles, m. p. 216° (Bucherer and Schmidt, *J. pr. Chem.*, 1909, 79, 375, give m. p. 216°) (Found : N, 5.4. Calc. for $C_{20}H_{12}N_2$: N, 5.2%).

Dinitration of 1 : 1'-Diacetamido-2 : 2'-dinaphthyl.—1 : 1'-Diacetamido-2 : 2'-dinaphthyl (0.95 g.) was stirred into nitric acid (25 c.c., *d* 1.42) below 15°. After 30 minutes' stirring, 4 : 4'-dinitro-1 : 1'-diacetamido-1 : 1'-dinaphthyl began to separate, and at this stage the mixture was poured into water (120 c.c.), and the precipitated dinitro-compound (0.5 g.) dissolved in a hot mixture of glacial acetic acid and xylene (1 : 1) from which it separated in light yellow micro-needles, m. p. 341—342° (Found : N, 12.5. $C_{24}H_{18}O_4N_4$ requires N, 12.3%). When this compound (1 g.) was refluxed for 10 hours with ethanol (10 c.c.) and sulphuric acid (10 c.c., *d* 1.08), and the mixture poured into water, there separated 3 : 6-dinitro-1 : 2 : 7 : 8-dibenzocarbazole which crystallised from nitrobenzene in yellow micro-crystals; these had no m. p. but sintered at ca. 385° (cf. Hodgson and Habeshaw, *loc. cit.*) (Found : N, 12.1. Calc. for $C_{20}H_{14}O_4N_4$: N, 11.8%).

The authors thank Imperial Chemical Industries Ltd. for various gifts.

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[Received, February 1st, 1947.]

311. The Formation of Hydroxythionaphthens by the Interaction of Benzenesulphonylbenzothiazolone and Substances containing a Reactive Methylene Group.

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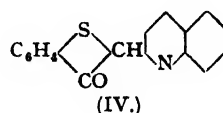
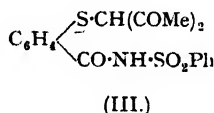
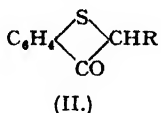
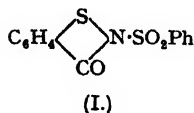
The isothiazolone (I) reacts with substances containing a reactive methylene group, in presence of pyridine or piperidine, with elimination of benzenesulphonamide, to give 2-substituted derivatives of 3-hydroxythionaphthen of type (II). The group R found in the product is the acetyl, propionyl or butyryl group with the respective aliphatic ketones, and the carbethoxy-group with ketonic esters, but reaction proceeds further in the case of acetone yielding a dithionaphthenyl ketone. Benzoylacetone and acetophenone yield 3-hydroxy-2-benzoylthionaphthen. α -Picoline and quinaldine give the 3-hydroxy-2-2'-pyridyl- and -quinolyl-thio-

naphthen. The mechanism of the reaction is discussed, the isolation of the substance (III) as the immediate product from acetylacetone being significant.

A remarkable reaction also occurs when the isothiazolone is heated with ethyl phenylacetate and pyridine or quinoline, pyridyl- or quinolyl-thionaphthen being produced.

THE work of Smiles and his collaborators (*J.*, 1912, 101, 570; 1915, 107, 1378; 1921, 119, 1810; 1924, 125, 876) showed that 3-hydroxythionaphthen and certain of its 2-derivatives could be prepared by warming together in sulphuric acid *o*-mercaptobenzoic acid and various substances such as malonic and acetoacetic esters, β -diketones, and malic or citric acid. The yields are, however, not always satisfactory, tarry by-products and thioindigotin being often present, and the reaction sometimes fails owing to the prior decomposition of the diketonic reagent.

It has now been found that the readily accessible benzenesulphonylbenzisothiazolone (I) reacts smoothly with various substances containing a reactive methylene group to produce good yields of 2-substituted derivatives of 3-hydroxythionaphthen (II), benzenesulphonamide being simultaneously eliminated.



The reaction with ethyl malonate, ethyl acetoacetate, or ethyl acetonedicarboxylate in presence of pyridine or piperidine gives 3-hydroxy-2-carbethoxythionaphthen (II, R = CO₂Et). When the thiazolone is heated with acetylacetone in boiling alcohol or toluene in the absence of any basic catalyst, a direct *addition compound* (III) results, which is converted by the action of alkalis or by heating in boiling pyridine into 3-hydroxy-2-acetylthionaphthen (II, R = COMe) and benzenesulphonamide: this same acetylthionaphthen is obtained directly when the original reaction with acetylacetone is conducted in boiling pyridine solution. The properties of the addition compound are consistent with structure (III), which is also supported by the analogy with the products of addition of the benzisothiazolone to aromatic amines, whose structure has been firmly established (McClelland and Peters, this vol., p. 1229).

From benzoylacetone the corresponding 3-hydroxy-2-benzoylthionaphthen (II, R = C(=O)Ph) is formed.

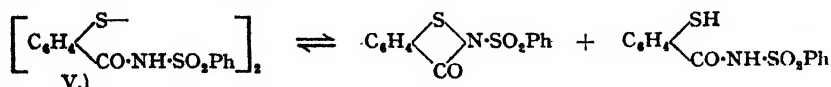
A reaction of the same kind takes place with ketones in general, but only in the presence of piperidine as catalyst. For instance, methyl ethyl ketone yields 3-hydroxy-2-propionylthionaphthen previously described by Krollpfeifer and Schneider (*Ber.*, 1928, 61, 1284), methyl *n*-propyl ketone gives 3-hydroxy-2-butyrylthionaphthen, and acetophenone the corresponding benzoylthionaphthen, while *m*-nitroacetophenone gives 3-hydroxy-2-*m*-nitrobenzoylthionaphthen.

With acetone the main product is 3:3'-dihydroxy-2:2'-dithionaphthenyl ketone (compare Friedländer and Risse, *Ber.*, 1914, 47, 1928) but a small amount of 3-hydroxy-2-acetylthionaphthen is obtained and may be an intermediate in the process. The latter substance does in fact condense further with the benzisothiazolone under the conditions of the reaction.

The reaction with diethyl ketone gave 3-hydroxy-2-methylthionaphthen, identified in the form of its oxidation product 2:2'-bis-(3-hydroxy-2-methylthionaphthen) (compare McClelland and D'Silva, *J.*, 1931, 2972), together with some 3-hydroxy-2-propionylthionaphthen, the formation of which seems inexplicable unless it was due to the presence of methyl ethyl ketone as an impurity.

Quinaldine and α -picoline also condense with benzenesulphonylbenzisothiazolone, yielding 3-hydroxy-2:2'-quinolylthionaphthen (IV), and the analogous pyridylthionaphthen.

Benzisothiazolone itself did not react with boiling acetone and its reaction with methyl ethyl ketone and quinaldine was slow. The benzisothiazolone when heated alone in boiling pyridine was reduced to di-*N*-benzenesulphonyl-2:2'-dithiobenzamide (V), and when the main condensation was slow (*e.g.*, with diethyl ketone) this disulphide (V) was sometimes found as a by-product. According to the dismutation theory (McClelland and Warren, *J.*, 1930, 1095; D'Silva and McClelland, *J.*, 1932, 2883) the disulphide and the benzisothiazolone are reversibly interconvertible thus:



It was found, in fact, that the dithiobenzamide (V) also condensed with acetylacetone slowly in boiling alcohol and somewhat faster in boiling pyridine.

No reaction could be detected between benzenesulphonylbenzisothiazolone and ethyl phenylacetate at 170° in presence of piperidine, but when pure quinoline was also present 3-hydroxy-2-2'-quinolylthionaphthen resulted, and with pyridine the analogous pyridylthionaphthen was again produced. These products were formed only when all three reactants were present, but the result has not been explained. When dimethylaniline was substituted for quinoline, an intensely blue substance was found in addition to 2-*N*-benzenesulphonylcarbonyl-4'-dimethylaminodiphenyl sulphide (cf. McClelland and Peters, *loc. cit.*), but its nature has not been elucidated.

EXPERIMENTAL.

Reactions of Benzenesulphonylbenzisothiazolone with Ketonic Substances.—Acetylacetone. The benzisothiazolone (5 g.) was heated in boiling ethyl alcohol (70 c.c.) with acetylacetone (3 g.) for 2 hours. On cooling, 3-(2'-benzenesulphonylcarbonylphenyl-1'-thio)pentane-2:4-dione (III) crystallised out (yield 94%). It forms white plates, m. p. 163° (decomp.) (Found: C, 55.1; H, 4.4; S, 16.6. $C_{11}H_{11}O_2NS_2$ requires C, 55.2; H, 4.4; S, 16.4%). This substance gives a red coloration with ferric chloride. It is soluble in benzene or hot methyl or ethyl alcohol but insoluble in ether or hot water. It was unchanged by heating in boiling toluene for 6 hours. Attempts to methylate, acetylate, or dehydrate it were unsuccessful. It dissolves in cold aqueous sodium hydroxide and is reprecipitated unchanged on acidification. After the alkaline solution had been boiled for $\frac{1}{2}$ hour it contained a thionaphthen, as shown by the formation of thioindigotin with potassium ferricyanide, and distillation of the solution in a current of steam yielded 3-hydroxy-2-acetylthionaphthen (m. p. 79°, not depressed by admixture of an authentic specimen), which was converted by phenylhydrazine into 1-phenyl-3-methyl-4:5-thionaphthenopyrazole, m. p. 120° (cf. Barry and McClelland, *J.*, 1935, 472). Benzenesulphonamide was deposited from the solution on cooling.

The addition compound yielded the same acetylthionaphthen when boiled in pyridine for 2 hours or heated at 40° for 4 hours with concentrated sulphuric acid.

Good yields of the same product were obtained direct by heating the benzisothiazolone with acetylacetone in pyridine for 3 hours.

The corresponding reaction of 1-*p*-toluenesulphonylbenzisothiazolone with acetylacetone in alcohol yielded 3-(2'-*p*-toluenesulphonylcarbonylphenyl-1'-thio)pentane-2:4-dione, white plates, m. p. 180° (decomp.), from alcohol (Found: C, 56.4; H, 4.6. $C_{10}H_{10}O_2NS_2$ requires C, 56.3; H, 4.7%), which on being heated in pyridine gave the 3-hydroxy-2-acetylthionaphthen and *p*-toluenesulphonamide.

Condensation of the benzisothiazolone with the diketonic substances, with pyruvic acid, and with *m*-nitroacetophenone was carried out by boiling equimolecular quantities together in pyridine. The reaction with ketones (4–6 mols., or an excess as solvent) took place in presence of a few drops of piperidine, the ketone itself or chloroform being used as solvent. Benzenesulphonamide was isolated as a by-product in every case.

Ethyl malonate. This did not react with the thiazolone in the absence of a basic catalyst. The mixture, after 4 hours' heating in boiling pyridine, was poured into dilute acid. The precipitated oil solidified, and was distilled in a current of steam. 3-Hydroxy-2-carbethoxythionaphthen was thus isolated (yield 79%); it separated from alcohol in white plates, m. p. 74° (Found: C, 58.9; H, 4.2. Calc.: C, 59.5; H, 4.5%) (cf. Arndt, Hirsch, and Nachtwey, *Ber.*, 1926, 59, 1077). Hydrolysis by 2*N*-sodium hydroxide at 100° yielded 3-hydroxythionaphthen, m. p. 70°, further converted into the thionaphthindole of m. p. 251° (McClelland and D'Silva, *J.*, 1932, 229).

Ethyl acetoacetate. This ester gave 3-hydroxy-2-carbethoxythionaphthen (yield 80%). When this was distilled in steam, a tarry residue was left from which cold alcohol separated some yellow 3:5'-dihydroxy-1:1'-dithionaphthenyl ketone which constitutes the main product from acetone.

When the reaction was carried out in ethyl alcohol with a little pyridine as catalyst the carbethoxythionaphthen and unchanged thiazolone were alone isolated, showing that the intermediate compound is unstable under these conditions.

Benzoyl acetone. The reaction mixture after 6 hours' boiling in pyridine was poured into dilute acid. The solid precipitated was distilled in a current of steam, to remove unchanged diketone, and then extracted with hot alcohol, from which 3-hydroxy-2-benzoylthionaphthen was deposited in yellow needles, m. p. 116 (Smiles and Ghosh, *J.*, 1915, 107, 1378).

Acetone. When the benzisothiazolone had been heated in boiling acetone with 2 drops of piperidine for 4 hours, yellow needles, m. p. 234°, were deposited which were identified as 3:3'-dihydroxy-2:2'-dithionaphthenyl ketone (Friedländer and Risse, *loc. cit.*) (Found: C, 62.7; H, 3.2; S, 19.6. Calc.: C, 62.6; H, 3.1; S, 19.7%), giving the diacetyl derivative, m. p. 183° (Found: C, 61.2; H, 3.3. Calc.: C, 61.5; H, 3.4%). A little 3-hydroxy-2-acetylthionaphthen was also found.

When the benzisothiazolone (2 g.) was heated in boiling benzene (100 c.c.) with the hydroxyacetylthionaphthen (1.5 g.) and 2 drops of piperidine for 7 hours the same dithionaphthenyl ketone was produced (yield 68%).

Methyl ethyl ketone. Under similar conditions this ketone furnished 3-hydroxy-2-propionylthionaphthen, m. p. 74° (Krollpfeifer and Schneider, *loc. cit.*) (Found: C, 64.3; H, 5.1. Calc.: C, 64.1; H, 4.9%) (yield 57%, but this was improved by warming the mixture for 5 minutes and keeping it for 10 days).

*Methyl *n*-propyl ketone.* The benzisothiazolone was boiled with the ketone and 6 drops of piperidine in chloroform solution for 7 hours. The mixture was diluted with ether, the solution washed successively with dilute acid and water, and evaporated. When the residue was distilled in a current of steam, the oil which came over solidified, and the 3-hydroxy-2-*n*-butyrylthionaphthen crystallised from

methyl alcohol in white needles, m. p. 36° (Found: C, 65.5; H, 5.7. $C_{15}H_{11}O_2S$ requires C, 65.5; H, 5.5%). This substance is slightly soluble in aqueous sodium hydroxide and slowly gives thio-indigotin on shaking with alkaline ferricyanide. It gives a greenish-violet ferric chloride reaction. This and the preceding propionyl compound failed to react with phenylhydrazine in boiling alcohol in presence of a little sulphuric acid after 6 hours' heating.

Acetophenone. After the reaction, the excess of ketone was removed in a current of steam. The residue was 3-hydroxy-2-benzoylthionaphthen, crystallising from alcohol in pale yellow needles, m. p. 117° (Smiles and Ghosh, *loc. cit.*).

Pyruvic acid. The product from the condensation, isolated by pouring into acid and collecting the precipitate, was 3-hydroxythionaphth-2-ylglyoxylic acid, yellow plates, m. p. 174°, after drying at 100° (Hart and Smiles, *J.*, 1924, 125, 876).

m-Nitroacetophenone. After 6 hours' boiling of the reaction mixture, the product crystallised on cooling. It was collected, and washed with pyridine, dilute acid, and water. 3-Hydroxy-2-m-nitro-benzoylthionaphthen crystallises from alcohol in pale yellow needles, m. p. 203° (Found: C, 60.0; H, 2.9; N, 5.1. $C_{15}H_{11}O_4NS$ requires C, 60.2; H, 3.0; N, 4.7%).

Diethyl ketone. The thiazolone was heated for 12 hours in boiling diethyl ketone with a little piperidine, the solvent evaporated, and the residue distilled in steam. The oil which slowly distilled was collected in ether, dried (Na_2SO_4), and the solvent evaporated. 3-Hydroxy-2-methylthionaphthen was thus isolated as a yellow viscous oil soluble in aqueous sodium hydroxide. It was converted by hot alkaline ferricyanide into 2:2'-bis-(3-hydroxy-2-methylthionaphthen), m. p. 151° (cf. McClelland and D'Silva, *loc. cit.*), and by hydrogen peroxide in glacial acetic acid into the dioxide, m. p. 110°. Further steam distillation after acidification of the mixture yielded a little 3-hydroxy-2-propionylthionaphthen, m. p. 70°, while benzenesulphonamide and di-N-benzenesulphonyl-2:2'-dithiobenzamide, m. p. 226°, were found in the mother-liquor.

Ethyl acetonedicarboxylate. This ester condensed with the benzisothiazolone on boiling in chloroform for 7 hours with a little piperidine. The solution was evaporated, and the residue acidified and distilled in a current of steam, whereupon 3-hydroxy-2-carbethoxythionaphthen came over (yield 86%).

Reaction of Benzenesulphonylbenzisothiazolone with Quinaldine and α -Picoline.—The thiazolone (4 g.) was boiled in chloroform (30 c.c.) for 6 hours with quinaldine (4 g.) and 2 drops of piperidine, the solution evaporated, and the excess of base removed in a current of steam. The remaining solid (yield 92%) was 3-hydroxy-2-2'-quinolylthionaphthen (IV), which crystallised from benzene in ruby-red prisms, m. p. 184° (Found: C, 73.6; H, 4.1; N, 5.2. $C_{17}H_{11}ONS$ requires C, 73.6; H, 4.0; N, 5.1%). Similar results but lower yields were obtained by using pyridine or glacial acetic acid as solvent. This substance is soluble in alcohol, chloroform, or hot acetic acid, giving blood-red solutions. It turns yellow with alkali or concentrated mineral acids, dissolving in the latter. Hydrochloric acid produced an unstable yellow substance, m. p. 117°, presumably a hydrochloride, which was reconverted into the parent substance by water.

Oxidation with ferricyanide in piperidine solution produced a white amorphous solid (purified from hot nitrobenzene) of m. p. 273° (sublimes). This is 2:2'-bis-(3-hydroxy-2-2'-quinolylthionaphthen) (Found: C, 73.7; H, 3.8. $C_{34}H_{20}O_6N_2S_2$ requires C, 73.9; H, 3.6%). The acetyl derivative of (IV) forms white plates, m. p. 177°, from acetic anhydride (Found: C, 71.4; H, 4.0. $C_{17}H_{11}O_3NS$ requires C, 71.5; H, 4.1%) and is hydrolysed rapidly by acids or alkalis and slowly by water or boiling alcohol.

The thiazolone was boiled with half its weight of α -picoline in glacial acetic acid for 5 hours. The product, which separated on cooling (yield 83%), crystallised from alcohol in fawn needles, m. p. 132°, of 3-hydroxy-2-2'-pyridylthionaphthen (Found: C, 68.8; H, 3.9. $C_{15}H_9ONS$ requires C, 68.7; H, 4.0%). A similar result was obtained by heating the thiazolone with α -picoline hydrochloride in boiling pyridine, but when the reagents were heated in chloroform with piperidine or in picoline alone as solvent the product was di-N-benzenesulphonyl-2:2'-dithiobenzamide.

The hydroxypyridylthionaphthen is soluble in hot alcohol or acetic acid or hot aqueous sodium hydroxide. It gives a yellow solution in mineral acids. It is slightly volatile in steam. Its acetyl derivative crystallises from acetic anhydride in massive white prisms, m. p. 133° (considerably depressed by adding the parent substance) (Found: C, 66.9; H, 4.0. $C_{15}H_{11}O_3NS$ requires C, 66.9; H, 4.1%).

Reaction of Unsubstituted Benzisothiazolone with Ketones and Quinaldine.—No reaction was detected when benzisothiazolone was boiled for 12 hours in acetone in presence of piperidine. With methyl ethyl ketone a very little hydroxypropionylthionaphthen was formed. With quinaldine after 8 hours' boiling in glacial acetic acid the hydroxyquinolylthionaphthen was produced in 32% yield.

Condensation with Ethyl Phenylacetate.—This ester (10 g.) would not react with benzenesulphonylbenzisothiazolone (5 g.) in presence of piperidine at 170°, but when pure quinoline (10 g.) was also present reaction had occurred after 5 hours' heating. The excess of reagents and solvent was removed from the red mixture in a current of steam, and the tarry product extracted with hot aqueous sodium hydroxide. The solution was decanted, cooled, and saturated with carbon dioxide. The red precipitate proved to be 3-hydroxy-2-2'-quinolylthionaphthen, m. p. 189° (yield 42%), and benzenesulphonamide was present in the mother-liquors.

In the same way benzenesulphonylbenzisothiazolone, heated with an equal weight of ethyl phenylacetate in boiling pure pyridine for 7 hours, gave 3-hydroxy-2-2'-pyridylthionaphthen, m. p. 133° (yield 39%), and the benzenesulphonyldithiobenzamide. No hydroxyphenylthionaphthen could be detected in these reactions.

The benzenesulphonylbenzisothiazolone also reacted when heated for 5 hours at 170° with ethyl phenylacetate and dimethylaniline in presence of piperidine. The products isolated immediately were benzenesulphonamide, the benzenesulphonyldithiobenzamide, 2-N-benzenesulphonylcarbonyl-4'-dimethylaminodiphenyl sulphide, m. p. 172°, and an intensely blue substance remained in the mother-liquor. This was collected chromatographically on anhydrous alumina, removed in alcohol, and recovered as a blue solid which separates from chloroform-petroleum in blue plates with a golden iridescence, m. p. 198°. It is stable to alkalis, gives yellow solutions in acids, and with hydrogen peroxide

in acetic acid yields a substance of m. p. 214°. The formation of this blue compound requires the presence of the thiazolone, the ester, the dimethylaniline, and the catalyst, but it was also observed when 2 : 2'-dithiobenzoic acid replaced the first of these or when benzyl cyanide replaced the ester.

Di-N-benzenesulphonyl-2 : 2'-dithiobenzamide as a Possible Intermediate in the Reactions.—Benzenesulphonylbenzothiazolone, boiled for 2 hours in pyridine, gave the dithiobenzamide, m. p. 226° (yield 60%).

The dithiobenzamide (0.5 g.), heated for 2 hours in boiling alcohol with acetylacetone (0.3 g.), gave, in addition to some recovered dithiobenzamide, 3-(2'-benzenesulphonylcarbamyphenyl-1'-thio)pentane-2 : 4-dione, m. p. 163° (yield 29%).

The dithiobenzamide, heated in boiling pyridine for 3 hours with acetylacetone (2 mols.), gave 3-hydroxy-2-acetylthionaphthen (yield 44%) and benzenesulphonamide.

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[Received, February 4th, 1947.]

312. Researches on Acetylenic Compounds. Part XI. The Mannich Reaction with Monosubstituted Acetylenic Compounds.

By E. R. H. JONES, I. MARSZAK, and (in part) H. BADER.

The scope of the Mannich reaction with mono-substituted acetylenic compounds, previously only applied to activated substances such as phenyl- and vinyl-acetylenes, has been extended to include alkylacetylenes and several types of acetylenic alcohols. Excellent yields are obtainable except with the α -ethynylcarbinols [containing the grouping $>C(OH)\cdot C\equiv CH$], but their acetates react normally. No suggestions for this anomalous behaviour can as yet be offered.

THE application of the well-known Mannich reaction (for summary see Blicke, "Organic Reactions," 1942, I, p. 303) in the acetylenic series has hitherto been restricted to compounds containing an activated ethynyl group, *e.g.*, phenyl- and substituted phenyl-acetylenes (Mannich and Chang, *Ber.*, 1933, 66, 418) and vinylacetylene (Coffman, *J. Amer. Chem. Soc.*, 1935, 57,



1978; Carothers and du Pont, U.S.P. 2,110,199). With acetylene itself the reaction has to be effected under pressure in the presence of a copper acetylide catalyst, under which conditions propargylamines ($HC\equiv C\cdot CH_2\cdot NR_2$) and the corresponding diamines are formed, the former preponderating (I.G. Farb., B.P. 510,904; U.S.P. 2,273,141).

The present study was undertaken with a view to extending the scope of the Mannich reaction to various types of acetylenic compounds. During the progress of this work information became available that some similar studies had been made in Germany (B.I.O.S. Final Report No. 266; item No. 22) and although no experimental details are available, it seems that copper catalysts were invariably employed.

In all the reactions described in this paper the appropriate reagents were heated in dioxan solution at about 80° in nitrogen. 1-Hexyne, the only hydrocarbon examined, gave a 75% yield of 1-diethylaminohept-2-yne (I). α -Ethynylcarbinols of type (II), invariably gave exceed-



ingly poor yields of the expected amines, but their acetates on the other hand behaved normally and yields of amines (III) ranging from 50 to 90% were obtained with the acetates of representative primary, secondary, and tertiary carbinols. The inhibiting effect of the hydroxyl group is apparently restricted to the α -position since the β -ethynylcarbinol [$CH_2\cdot CH(OH)\cdot CH_2\cdot C\equiv CH$] gave a 60% yield of amine. With conjugated ethynyl-ethylenic carbinols such as (IV) no inhibiting effect of the hydroxyl groups was observed, 80–85% yields of the expected amines being achieved both with the carbinols themselves and with their acetates. The products in these cases all exhibited similar light absorption properties in the ultra-violet, arising from the presence of the conjugated ethylenic-acetylenic chromophore.

The partial and complete hydrogenation and also other reactions of the acetylenic amino-alcohols described in this paper are being studied and will be reported on in a subsequent communication.

EXPERIMENTAL.

Light-absorption data were determined in alcoholic solutions.

1-Diethylaminohept-2-yne (I).—To a warm solution of diethylamine (16 g.) and trioxymethylene (7.2 g.) in dioxan (20 c.c.), a solution of 1-hexyne (16.4 g.) in dioxan (10 c.c.) was added and the mixture

was heated on a steam-bath for 15 hours in an atmosphere of nitrogen. Ether was added, and the basic product was isolated by washing with 2*N*-hydrochloric acid and then liberated with sodium hydroxide (10%). After ether extraction, drying (Na_2SO_4), and evaporation, distillation gave 1-diethylaminohept-2-yne (25.7 g.; 77%), b. p. $100^\circ/20$ mm., n_D^{25} 1.4513 (Found: C, 78.95; H, 12.5. $\text{C}_{11}\text{H}_{21}\text{N}$ requires C, 78.95; H, 12.6%). The *picrate*, prepared in methanol, crystallised from this solvent as long prisms, m. p. 75° (Found: C, 51.8; H, 6.2. $\text{C}_{17}\text{H}_{24}\text{O}_7\text{N}_4$ requires C, 51.5; H, 6.1%).

1-Dimethylamino-4-acetoxyprop-2-yne.—A mixture of dimethylamine (6 g.), trioxymethylene (4.7 g.), and propargyl acetate (12 g.) in dioxan (25 c.c.) was heated for 34 hours on a steam-bath. The *amine* (8.8 g.) had b. p. $65^\circ/0.7$ mm., n_D^{25} 1.4531 (Found: C, 61.55; H, 8.85. $\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ requires C, 61.9; H, 8.45%). The *methiodide* crystallised from methanol-ether in prisms, m. p. 140° (Found: C, 36.75; H, 5.55. $\text{C}_8\text{H}_{14}\text{O}_2\text{NI}$ requires C, 36.35; H, 5.45%).

1-Diethylamino-4-acetoxyhept-2-yne (III; R = H; $\text{R}_1 = n\text{-Pr}$).—The standard method (20 hours' heating) employed with diethylamine (8 g.), trioxymethylene (3.9 g.), and 3-acetoxyhex-1-yne (14 g.; Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 45) in dioxan (15 c.c.) gave the *amine* (20 g.), b. p. $81^\circ/0.1$ mm., n_D^{25} 1.4546 (Found: C, 69.2; H, 10.4. $\text{C}_{13}\text{H}_{23}\text{O}_2\text{N}$ requires C, 69.25; H, 10.3%). The same base was obtained, but in poorer yield, by carrying out the reaction at 20° . The *oxalate* crystallised from ethanol-ether as fine prisms, m. p. 90.5° (Found: C, 57.2; H, 7.65. $\text{C}_{11}\text{H}_{23}\text{O}_6\text{N}$ requires C, 57.1; H, 8.0%).

1-Diethylamino-1'-acetoxy-3-cyclohexylprop-2-yne (III; $\text{RR}' = \text{C}_6\text{H}_{10}$).—Diethylamine (12 g.), trioxymethylene (5.4 g.), and ethynylcyclohexanyle acetate (24.9 g.) in dioxan (25 c.c.) after being heated for 30 hours gave the *amine* (29.7 g.), b. p. $111^\circ/0.6$ mm., n_D^{25} 1.4806 (Found: C, 71.95; H, 10.25. $\text{C}_{15}\text{H}_{25}\text{O}_2\text{N}$ requires C, 71.65; H, 10.05%). The *picrate* crystallised from methanol in plates, m. p. 114° (Found: C, 52.6; H, 5.9. $\text{C}_{21}\text{H}_{29}\text{O}_8\text{N}_4$ requires C, 52.45; H, 5.9%).

1-Diethylaminohex-2-yn-5-ol.—After a mixture of diethylamine (12.4 g.), trioxymethylene (6.75 g.), and pent-1-yn-4-ol (12.6 g.; Haynes and Jones, *J.*, 1946, 956) had been heated on a steam-bath for 30 hours, the *amine* (15 g.) was isolated with b. p. $73^\circ/0.1$ mm., n_D^{25} 1.4740 (Found: C, 71.0; H, 11.45. $\text{C}_{10}\text{H}_{19}\text{ON}$ requires C, 70.95; H, 11.3%). The *picrate* crystallised from benzene in prisms, m. p. 78° (Found: C, 48.4; H, 5.65. $\text{C}_{16}\text{H}_{23}\text{O}_6\text{N}_4$ requires C, 48.2; H, 5.55%).

1-Diethylaminohex-4-en-2-yn-6-ol.—A mixture of diethylamine (16 g.), trioxymethylene (7.2 g.), and pent-2-en-4-yn-1-ol (16.4 g.; Haynes, Heilbron, Jones, and Sondheimer, Part XIII, this vol., p. 1583) in dioxan (25 c.c.) on being heated for 25 hours on a steam-bath gave the *amine* (25.4 g.), b. p. $135^\circ/1$ mm., n_D^{25} 1.5102 (Found: C, 72.1; H, 10.25. $\text{C}_{10}\text{H}_{17}\text{ON}$ requires C, 71.8; H, 10.25%). Light absorption: Maximum, 2270 Å.; $\epsilon = 15,500$. Inflection, 2370 Å., $\epsilon = 12,500$. The *a-naphthylurethane* crystallised from petroleum (b. p. $80\text{--}100^\circ$) in plates, m. p. 79° (Found: C, 75.05; H, 7.4. $\text{C}_{21}\text{H}_{26}\text{O}_2\text{N}_2$ requires C, 74.95; H, 7.2%).

1-Diethylaminohex-4-en-2-yn-6-ol.—The standard method (36 hours' heating) employed with diethylamine (12.4 g.), trioxymethylene (6 g.), and hex-3-en-5-yn-2-ol (13.8 g.; Heilbron, Jones, and Weedon, *J.*, 1945, 81) in dioxan (20 c.c.) gave the *amine* (21 g.), b. p. $85^\circ/0.1$ mm., n_D^{25} 1.5003 (Found: C, 73.1; H, 10.75. $\text{C}_{11}\text{H}_{19}\text{ON}$ requires C, 72.85; H, 10.55%). Light absorption: Maximum, 2270 Å.; $\epsilon = 15,000$. Inflection, 2350 Å.; $\epsilon = 13,000$. The *picrate*, prepared in methanol, crystallised from benzene in plates, m. p. 118° (Found: C, 49.95; H, 5.55. $\text{C}_{17}\text{H}_{22}\text{O}_6\text{N}_4$ requires C, 49.75; H, 5.4%).

1-Dimethylamino-6-acetoxyhept-4-en-2-yne.—A mixture of dimethylamine (5 g.), trioxymethylene (3.6 g.), and 2-acetoxyhex-3-en-5-yne (13.8 g.; Jones and McCombie, *J.*, 1943, 261) in dioxan (30 c.c.) after being heated for 24 hours on a steam-bath gave the *amine* (16.2 g.), b. p. $72^\circ/0.5$ mm., n_D^{25} 1.4808 (Found: C, 68.15; H, 8.7. $\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}$ requires C, 67.65; H, 8.8%). The *methoperchlorate* crystallised from methanol-ether in plates, m. p. 112.5° (Found: C, 46.75; H, 6.35. $\text{C}_{11}\text{H}_{20}\text{O}_6\text{NCl}$ requires C, 46.5; H, 6.5%).

1-Diethylamino-6-acetoxyhept-4-en-2-yne.—Prepared as above using diethylamine (8 g.) instead of dimethylamine, the *amine* (19.1 g.) had b. p. $108\text{--}110^\circ/1$ mm., n_D^{25} 1.4800 (Found: C, 69.5; H, 9.4. $\text{C}_{13}\text{H}_{21}\text{O}_2\text{N}$ requires C, 69.9; H, 9.5%).

The authors thank Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement and Dr. E. A. Braude for the light-absorption data.

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[Received, January 18th, 1946.]

313. Researches on Acetylenic Compounds. Part XII. The Preparation of Conjugated Diacetylenic Glycols by the Oxidative Coupling of Various Types of Ethynylcarbinols.

By K. BOWDEN, SIR IAN HEILBRON, E. R. H. JONES, and K. H. SARGENT.

Contrary to the experiences of earlier workers it has now been found that the coupling of ethynylcarbinols to diacetylenic glycols, by aerial oxidation in the presence of cuprous ammonium chloride, is a general reaction applicable to carbinols of various types. The scope of synthetic reactions with acetylenic compounds is thereby considerably extended, and these interesting glycols become readily available for more detailed study. Moreover, the function of the cuprous salt appears to be largely catalytic, and coupling can be effected with the use of much less than one equivalent of cuprous ammonium chloride. Light-

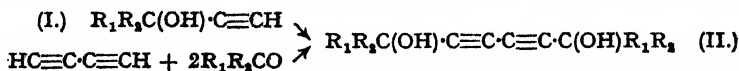
absorption data for the conjugated diacetylene chromophore are recorded and compared with those of conjugated diene and vinylacetylene systems.

THE formation of diacetylenes by the oxidative coupling of metallic derivatives of mono-substituted acetylenes was first observed as early as 1869, and several alternative procedures have since been described. These mainly involve oxidation of either the cuprous or the



halogenomagnesium acetylides with agents such as oxygen, ferricyanide, cupric salts, etc. (For summary and references see "The Chemistry of Acetylene," Nieuwland and Vogt, Reinhold, New York, 1945.) Cupric acetylides are apparently unstable, and, in all reactions in which they should be produced, coupling to diacetylenes occurs.

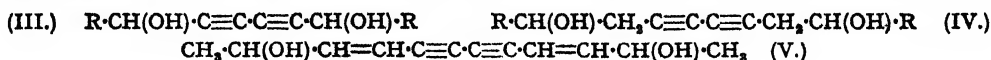
The oxidation of the readily-available ethynylcarbinols (*e.g.*, I) is of particular importance and interest since it provides facile synthetic routes to bifunctional compounds difficult to prepare by other means. This is especially true since the only alternative route to the



diacetylenic glycols (II), *i.e.*, via diacetylene, is ruled out because of the practical difficulties involved in preparing this hydrocarbon in quantity. It should be noted, however, that diacetylene has become available in Germany in recent years as a by-product (7%) in the Huels arc process for the production of acetylene from gaseous hydrocarbons.

Zal'kind and his collaborators (*J. Gen. Chem. Russia*, 1937, 7, 227; 1939, 9, 971, 1725; *Ber.*, 1936, 69, 128) reported that aerial oxidation of the cuprous acetylides of tertiary ethynylcarbinols at room temperature gave good yields of the corresponding diacetylenic glycols, but that only very indifferent yields could be obtained with secondary ethynylcarbinols. These authors sought a theoretical explanation of this lack of reactivity of the secondary carbinols in terms of the opposing inductive effects of the hydroxyl and alkyl groups involved.

It has now been ascertained that by carrying out the aerial oxidation at somewhat higher temperatures, *e.g.* in the range 50–70°, coupling of a wide variety of ethynylcarbinols can be achieved, in most cases to give excellent yields. Methyl-, propyl-, and phenyl-ethynylcarbinols give the secondary glycols (III; R = Me, Pr, and Ph respectively) as mixtures of the *dl*- and *meso*-forms. The reaction can be extended to carbinols made from alkylene oxides giving the glycols (IV; R = H and Me), the latter again probably as a mixture of stereoisomerides. The



glycol derived from ethylene oxide (*i.e.*, IV; R = H), the structure of which has been proved by hydrogenation to octane-1:8-diol, is remarkably unstable, being very readily converted into a scarlet insoluble pigment by what appears to be a photo-catalysed oxidation.

Not only can simple ethynylcarbinols be coupled up by this process, but even conjugated ethynylethylenic carbinols such as hexenynol [$CH_3\cdot CH(OH)\cdot CH=CH\cdot C\equiv CH$] can be oxidised. The glycol (V) obtained from this carbinol is a crystalline solid, presumably stereochemically pure, and its structure is proved by its hydrogenation to dodecane-2:11-diol, which on oxidation gives sebacic acid. Another example of this type is furnished in Part XIV (p. 1586) where the light-absorption data for the chromophore present in glycols such as (V) are discussed.

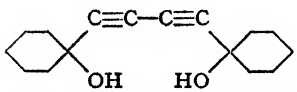
In addition to demonstrating the general nature of this oxidative coupling reaction, it has also been shown, contrary to earlier work in this field, that it is unnecessary to employ a large excess of cuprous ammonium chloride. While this work was in progress information became available that the I.G. Farb. at Ludwigshafen had effected the oxidation of propargyl alcohol to hexadienediol using only catalytic quantities of cuprous salt. Three representative glycols (II, R₁ = Me, R₂ = Et; II, R₁R₂ = CH₃ < [CH₂]₄ >; and III, R = Pr) have been prepared in this way, by employing 0.2–0.5 equivalent of cuprous chloride. Although the process is rendered somewhat slower and higher reaction temperatures have to be employed, the yields remain excellent.

The light-absorption properties of the diacetylenic glycols, recorded in the accompanying Table, agree with those previously determined for 2:7-dimethylocta-3:5-diyne-2:7-diol (II; R₁ = R₂ = Me) (mentioned by Jones and McCombie, *J.*, 1943, 261). The conjugated diacetylene chromophore exhibits absorption at rather longer wave-lengths than conjugated vinylacetylenes and dienes, but the intensities are only of a very low order. The progressive

diminution in intensity and the accompanying appearance of fine structure in the conjugated diene, en-yne, and di-yne systems is of some interest.

Various aspects of the chemistry of these readily accessible diacetylenic glycols are at present being studied in these laboratories.

Light-absorption data of conjugated diacetylenic glycols compared with those of conjugated dienes and vinylacetylenes.

(In alcoholic solutions.)	$\lambda_{\text{max.}}, \text{\AA.}$	$\epsilon_{\text{max.}}$
$\text{CH}_3 \cdot \text{CH}=\text{CH} \cdot \text{CH}=\text{CH}_2$ ¹	2235	23,000
$\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CH}=\text{CH} \cdot \text{C}\equiv\text{CH}$ ²	2230	13,500
	2300 *	9,500
$\text{Me}_2\text{C}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{C}(\text{OH})\text{Me}_2$	2290	310
	2410	300
	2560	180
$\text{HO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH}$	2280	540
	2390	540
	2510	360
$\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_3$	2260	355
	2410	410
	2640	250
$\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CH}(\text{OH}) \cdot \text{CH}_3$ (m. p. 67°)	2300	1,930
	2370	1,860
$\text{C}_3\text{H}_7 \cdot \text{CH}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CH}(\text{OH}) \cdot \text{C}_3\text{H}_7$	2320	360
	2420	400
	2550	265
	2820 *	90
	2310	294
	2420	347
	2440	332
	2570	160
$\text{C}_2\text{H}_5 \cdot \text{CMe}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CMe}(\text{OH}) \cdot \text{C}_2\text{H}_5$	2300	330
	2420	368
	2550	204
$\text{C}_9\text{H}_{19} \cdot \text{CMe}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CMe}(\text{OH}) \cdot \text{C}_9\text{H}_{19}$	2400	515
	2420	
	2520	
	2680	
	2820	465
	3080 ³	135
$\text{Ph} \cdot \text{CH}(\text{OH}) \cdot \text{C}\equiv\text{C} \cdot \text{C}\equiv\text{C} \cdot \text{CH}(\text{OH}) \cdot \text{Ph}$	2460	1,150
	2600	785

* Inflexion.

¹ Booker, Evans and Gillam, *J.*, 1940, 1453.

² Jones and McCombie, *J.*, 1943, 261.

³ This band may arise from the presence of a small quantity of dehydrated material.

EXPERIMENTAL.

Octa-3:5-diyne-2:7-diol (III; R = Me).—Methylethynylcarbinol (37 g.) in ethanol (20 c.c.) was added to a mixture of cuprous chloride (100 g.), ammonium chloride (160 g.), hydrochloric acid (1 c.c.), and water (425 c.c.) at room temperature. The temperature was raised to 55° and air was passed in for 6½ hours, a condenser containing solid carbon dioxide and alcohol being used to prevent loss of carbinol. Isolation with ether and distillation gave a mixture of stereoisomers of octa-3:5-diyne-2:7-diol (31 g.), m. p. 84–87° (change of state at 65°), b. p. ca. 120°/10⁻⁴ mm. A single process of chromatography on 2 g. of this product gave one of the stereoisomeric forms (0.3 g.), m. p. 64–67° (Lespieau, *Ann. Chim.*, 1912, 27, 137, quotes m. p. 67.5–68° for one of the isomeric forms. The other has m. p. 108–109° according to Zal'kind and Gverdtsiteli, *J. Gen. Chem. Russia*, 1939, 9, 971).

Dodeca-5:7-diyne-4:9-diol (III; R = Pr).—(a) Propylethynylcarbinol (25 g.; Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 45) in ethanol (25 c.c.) was added dropwise during 15 minutes to a solution of ammonium chloride (160 g.), cuprous chloride (100 g.), and concentrated hydrochloric acid (1.5 c.c.) in water (450 c.c.) at 50–55°. The mixture was stirred for 15 minutes at this temperature; air was then passed in for 2 hours, by which time the mixture had assumed a deep greenish colour. After cooling, the product was isolated with ether and distilled from a Claisen flask with a low, wide side-arm giving the glycol (21.2 g.), b. p. 134°/10⁻³ mm., n_D^{25} 1.5178 (Zal'kind and Gverdtsiteli, *loc. cit.*, give b. p. 159–162°/7 mm.).

(b) Propylethynylcarbinol (5 c.c.) was added to a solution of ammonium chloride (16 g.), cuprous chloride (10 g.), and concentrated hydrochloric acid (0.15 c.c.) in water (45 c.c.) during 5 minutes. With the mixture at a temperature of 50–55°, air was passed in and a further 25 c.c. of the carbinol

was added dropwise during 1 hour. After oxidation for 8 hours precipitation of cupric salts commenced. Sufficient dilute hydrochloric acid was added to the cooled mixture to dissolve the solid, and isolation with ether gave the glycol (23 g.), b. p. $133^{\circ}/10^{-3}$ mm., n_D^{20} 1.5175. One of the stereoisomeric forms of the *bis-a-naphthylurethane* was isolated from the mixture of isomers by recrystallisation from ethanol. It formed needles, m. p. 158° (Found: N, 5.05. $C_{24}H_{20}O_4N_2$ requires N, 5.25%).

Dodecane-4: 9-diol.—Dodeca-5: 7-diyne-4: 9-diol (4.85 g.) in ethyl acetate (100 c.c.) was hydrogenated in the presence of platinum oxide (10 mg.) until absorption ceased. Removal of catalyst and solvent and crystallisation of the residual solid from light petroleum (b. p. $40-60^{\circ}$) gave *dodecane-4: 9-diol* (4.5 g.) as lustrous leaflets, m. p. 53° (Found: C, 71.45; H, 12.75. $C_{12}H_{24}O_2$ requires C, 71.25; H, 12.95%).

1: 6-Diphenylhexa-2: 4-diyne-1: 6-diol (III; R = Ph).—Phenylethynylcarbinol (25 g.; Jones and McCombie, *J.*, 1942, 733) in ethanol (50 c.c.) was added to a mixture of ammonium chloride (160 g.), cuprous chloride (100 g.), concentrated hydrochloric acid (1.5 c.c.), and water (450 c.c.) at $50-55^{\circ}$. Air was passed in for 2 hours; isolation with ether and crystallisation from benzene gave a mixture of stereoisomers as leaflets (12 g.), m. p. 102° . Repeated crystallisations from benzene gave matted needles with m. p. 122° (sintered at 90° and softened at 103°) (Zal'kind and Gverdtsitel, *loc. cit.*, give m. p. $132-133^{\circ}$).

Octa-3: 5-diyne-1: 8-diol (IV; R = H).—A solution of but-1-yn-4-ol (15 g.) (Macallum, U.S.P. 2,125,384) in ethanol (25 c.c.) was added to ammonium chloride (96 g.), cuprous chloride (60 g.), and concentrated hydrochloric acid (0.9 c.c.) in water (270 c.c.) during 20 minutes. Air was passed in at $50-55^{\circ}$ for 2 hours and after the mixture had been cooled and saturated with salt the product was isolated with ether, giving *octa-3: 5-diyne-1: 8-diol* (7.1 g.), m. p. $42-43^{\circ}$, b. p. $135^{\circ}/10^{-4}$ mm. The solid became scarlet on exposure to light and air and no satisfactory analytical data could be obtained (Found: C, 68.0; H, 7.1. $C_8H_{10}O_2$ requires C, 69.5; H, 7.3%). The *diacetate* crystallised from petroleum (b. p. $80-100^{\circ}$) in needles, m. p. 63° (Found: C, 64.85; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%). A solution of the diol (3.3 g.) in ethyl acetate (50 c.c.) was hydrogenated in the presence of platinum oxide (20 mg.) giving *octane-1: 8-diol* (3.0 g.), m. p. $60-61^{\circ}$ (from ethyl acetate) (Franke and Lieben, *Monatsh.*, 1914, 35, 1939, give m. p. 60°).

Deca-4: 6-diyne-2: 9-diol (IV; R = Me).—1-Pentyn-4-ol (25 g., Haynes and Jones, *J.*, 1946, 954) in ethanol (50 c.c.) was added to a mixture of ammonium chloride (160 g.), cuprous chloride (100 g.), concentrated hydrochloric acid (1.5 c.c.), and water (450 c.c.) at $50-55^{\circ}$ during 30 minutes. Air was then passed in for 135 minutes at $50-55^{\circ}$, and extraction of the cooled mixture with ether and distillation of the dried extract gave *deca-4: 6-diyne-2: 9-diol* (20.35 g.), b. p. $136^{\circ}/10^{-3}$ mm., n_D^{20} 1.5345. This material solidified at 0° but melted at room temperature (Found: C, 72.35; H, 8.7. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%). One of the stereoisomeric forms of the *bis-3: 5-dinitrobenzoate*, m. p. 192° , was isolated by fractional precipitation with petrol from an ethyl acetate solution of the mixture of isomers (Found: N, 10.0. $C_{22}H_{14}O_{12}N_4$ requires N, 10.1%).

Di-(1-hydroxycyclohexyl)butadiyne (II; $R_1R_2 = C_6H_{10}$).—3 C.c. of a solution of 1-ethynylcyclohexanol (25.2 g., Hennion and Murray, *J. Amer. Chem. Soc.*, 1942, 64, 1220) in ethanol (30 c.c.) were added to a solution of ammonium chloride (8 g.), cuprous chloride (2.5 g., 0.2 equivalent), and concentrated hydrochloric acid (0.5 c.c.) in water (25 c.c.) at 30° , and the mixture stirred for 5 minutes. The temperature was raised to 70° , air was passed in, the rest of the carbinol solution was added dropwise during $3\frac{1}{2}$ hours, and oxidation was continued for a further $4\frac{1}{2}$ hours. The mixture was poured into 300 c.c. of ammonium chloride solution and the precipitated solid completely freed from copper salts by washing it with *N*-hydrochloric acid followed by water. After being dried, this solid was recrystallised twice from benzene to give *di-(1-hydroxycyclohexyl)butadiyne* (23.5 g.), m. p. 173° (Zal'kind and Aizikovich, *J. Gen. Chem. Russia*, 1937, 7, 227, give m. p. 173°) (Found: C, 78.05; H, 8.85. Calc. for $C_{14}H_{22}O_2$: C, 78.0; H, 9.0%).

3: 8-Dimethyldeca-4: 6-diyne-3: 8-diol (II; $R_1 = Me$; $R_2 = Et$).—10 C.c. of a solution of methyl-ethynylethynylcarbinol (20.8 g.; Campbell, Campbell, and Eby, *J. Amer. Chem. Soc.*, 1938, 60, 2882) in ethanol (25 c.c.) were added to a solution of ammonium chloride (8 g.), cuprous chloride (2.5 g.), and concentrated hydrochloric acid (0.05 c.c.) in water (25 c.c.), and the mixture stirred for a minute at room temperature. The colour changed from brown to green. The temperature was raised to and maintained at $65-70^{\circ}$ whilst air was passed in at a rate of about 2 l. per minute. The remainder of the carbinol solution was added in 5 c.c. portions during the next 8 hours, and the oxidation was continued for a further 5 hours. The cooled mixture was poured into 200 c.c. of ammonium chloride solution and the resultant solid washed with dilute hydrochloric acid to give 14 g. of a solid, m. p. $80-88^{\circ}$. With 6 equivs. of cuprous ammonium chloride solution the yield is slightly better and the reaction takes only 2 hours. Solution of a portion (2 g.) in the minimum volume of ethyl acetate followed by partial precipitation with petroleum (b. p. $80-100^{\circ}$) gave one of the stereoisomeric forms (0.85 g.), m. p. 88° (I.G. Farb. F.P. 765,469 give m. p. 89°) (Found: C, 73.95; H, 9.25. Calc. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.35%).

Dodeca-3: 9-diene-5: 7-diyne-2: 11-diol (V) (with F. SONDHEIMER).—Hex-3-en-5-yn-2-ol (6 g.; Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 57) was slowly dropped into a stirred solution of ammonium chloride (80 g.) and cuprous chloride (50 g.) in water (200 c.c.), maintained at 55° . Air was bubbled through the red solution at this temperature for 2 hours during which time much black gum separated. The product isolated by repeated ether extraction contained much polymeric material from which it was separated by boiling with water. This furnished the *diol* (1.5 g.) as light yellow needles, m. p. 92° , which after recrystallisation from either water or benzene (nitrogen atmosphere) gave colourless needles, m. p. $94-95^{\circ}$ (Found: C, 75.5; H, 7.45. $C_{12}H_{18}O_2$ requires C, 75.75; H, 7.4%). The glycol slowly becomes yellow in air. Light absorption: see Part XIV, p. 1587.

Dodecane-2: 11-diol (with F. SONDHEIMER).—A solution of the above glycol (400 mg.) in methanol (20 c.c.) was shaken with hydrogen in the presence of platinum oxide (10 mg.) until absorption was complete. Crystallisation of the product from pentane-ether (3: 1) gave *dodecane-2: 11-diol* (350 mg.) as plates, m. p. $54-55^{\circ}$ (Found: C, 71.1; H, 12.85. $C_{12}H_{24}O_2$ requires C, 71.25; H, 12.95%). Oxid-

ation of the diol with chromic acid in sulphuric acid gave a 75% yield of dodecane-2 : 11-dione, leaflets from light petroleum (b. p. 40–60°), m. p. 67° (Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 48, give m. p. 87.4–87.8°). Sebacic acid, m. p. 130–131°, undepressed on admixture with an authentic specimen (m. p. 132°), was obtained when the diketone was shaken with sodium hypobromite solution for 48 hours at 20°.

10:15-Dimethyltetracos-11:13-diyne-10:15-diol (II; $R_1 = \text{Me}$; $R_2 = \text{C}_6\text{H}_{13}$).—Methylnonylethynylcarbinol (10 g.; Locquin and Sung, *Compt. rend.*, 1922, **174**, 1427) in ethanol (10 c.c.) was added to a mixture of ammonium chloride (64 g.), cuprous chloride (40 g.), concentrated hydrochloric acid (0.4 c.c.), and water (200 c.c.), and stirred at 65–67°. Oxygen was passed through at about 3 l. per minute, and after 45 minutes the reaction mixture was cooled, hydrochloric acid was added to dissolve copper salts, and the product was isolated with ether. Distillation gave the *glycol* (2.75 g.), b. p. 210°/10–3 mm., m. p. 40–43° (Found: C, 79.9; H, 11.7. $\text{C}_{26}\text{H}_{46}\text{O}_2$ requires C, 79.95; H, 11.85%). 5.4 G. of carbinol were recovered.

The authors thank the Rockefeller Foundation and I.C.I. Ltd., Dyestuffs Division, for financial assistance, and the Department of Scientific and Industrial Research for a maintenance grant (K. H. S.). Light-absorption data were determined by Dr. E. A. Braude.

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[Received, January 18th, 1947.]

314. Researches on Acetylenic Compounds. Part XIII. The Reaction Between Epichlorohydrin and Sodium Acetylide. A Novel Route to the Ethynyl-ethylenic Alcohol, Pent-2-en-4-yn-1-ol.*

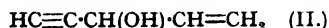
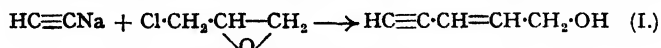
By L. J. HAYNES, SIR IAN HEILBRON, E. R. H. JONES, and F. SONDEIMER.

Condensation between epichlorohydrin and sodium acetylide in liquid ammonia gives, rather unexpectedly, the ethynyl-ethylenic primary alcohol, pentenynol (I). Evidence is adduced to show that this reaction proceeds *via* the ethynyl oxide (III); in particular, it is demonstrated that 1:2-epoxy-3-phenylpropane ($\text{Ph}\cdot\text{CH}_2\cdot\text{CH}(\text{O})\cdot\text{CH}_2$) is isomerised to cinnamyl

alcohol by treatment with sodamide in liquid ammonia. Analogous condensations with the sodio-derivatives of 1-hexyne and phenylacetylene give similar products, albeit in poorer yields.

IN connexion with the synthesis of various types of acetylenic hydroxy-acids and the derived unsaturated lactones (Haynes and Jones, *J.*, 1946, 503 and 954) the condensation of various oxides or epoxy-compounds with sodium acetylide in liquid ammonia has been investigated. This paper describes some rather unexpected results which were obtained when epichlorohydrin was employed in such reactions. There is only one instance in the literature of the reaction of epichlorohydrin with an acetylenic compound, namely phenylacetylenylmagnesium bromide (Iotsitch, *J. Russ. Phys. Chem. Soc.*, 1903, **35**, 554), when a normal addition product, either $\text{Ph}\cdot\text{C}\equiv\text{C}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{Cl}$ or $\text{Ph}\cdot\text{C}\equiv\text{C}\cdot\text{CH}(\text{CH}_2\text{Cl})\cdot\text{CH}_2\cdot\text{OH}$, was obtained in poor yield.

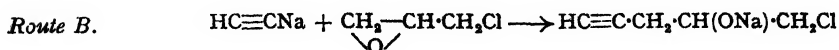
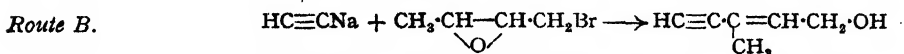
When epichlorohydrin reacts with sodium acetylide in liquid ammonia, the sole product, obtained in about 40% yield, is the ethynylethylenic alcohol, pent-2-en-4-yn-1-ol (I). This substance had already been prepared in these laboratories in extremely poor overall yield from



acetaldehyde *via* vinyl ethynylcarbinol (II) (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77). The yield of the primary alcohol, based on the epichlorohydrin, is markedly dependent on the quantity of sodium acetylide employed. Thus with equimolar quantities of chlorohydrin and sodium under standard conditions, the yield is only 16%, but it is not improved beyond 40% when more than two moles of sodium to one of chlorohydrin are employed. Varying the reaction time from 5 to 18 hours has no appreciable effect upon the yield, and this was considerably reduced in an experiment in which the reaction mixture was kept under pressure at room temperature for 18 hours. When epibromohydrin is used under the optimum conditions found for the chlorohydrin, only a 25% yield of pentenynol is obtained. With sodium acetylide in liquid ammonia epi-iodohydrin yields mainly di-iodoacetylene.

The formation of pentenynol (I) from epichlorohydrin can conceivably take place by either of two routes, A and B, depending upon whether the initial reaction step is one of substitution or

* Patent application pending.

$$\begin{array}{c} \text{Route A.} \quad \text{HC}\equiv\text{CNa} + \text{Cl}\cdot\text{CH}_2\cdot\underset{\text{O}}{\text{CH}}\cdot\text{CH}_2 \cdot \rightarrow \text{HC}\equiv\text{C}\cdot\text{CH}_2\cdot\underset{\text{O}}{\text{CH}}\cdot\text{CH}_2 \quad (\text{III.}) \\ \downarrow \\ \text{HC}\equiv\text{C}\cdot\text{CH}=\text{CH}\cdot\text{CH}_2\cdot\text{OH} \quad (\text{I.}) \\ \uparrow \end{array}$$

$$\text{Route A. } \text{HC}\equiv\text{CNa} + \text{Br}\cdot\text{CH}_2\text{CH}(\text{OH})\text{CH}_3 \text{ (IV.)} \longrightarrow \text{HC}\equiv\text{C}\cdot\text{CH}=\text{CH}\cdot\text{CH}(\text{OH})\cdot\text{CH}_3 \text{ (V.)}$$

$$(VI.) \quad \text{Ph} \cdot \text{CH}_2 \cdot \underset{\text{O}}{\text{CH} - \text{CH}_2} \longrightarrow \text{Ph} \cdot \text{C} \equiv \text{HCH} \cdot \text{CH}_2 \cdot \text{OH}$$

Attempts to extend the scope of the novel reaction between epichlorohydrin and sodium acetylide, by using substituted acetylenes, have not been particularly successful. Thus phenylacetylene gives only a 15% yield of the primary alcohol (5-phenylpent-2-en-4-yn-1-ol) (VII), the structure of which is confirmed by the ultra-violet absorption data and by



EXPERIMENTAL.

Pent-2-en-4-yn-1-ol (I).—(a) To a solution of sodium acetylide in liquid ammonia (7 l.), prepared from sodium (276 g.), using the ferric nitrate catalyst of Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) to catalyse the formation of sodamide, epichlorohydrin (555 g.) was run in during 2 hours with stirring and cooling (alcohol-carbon dioxide). Nitrogen was introduced during the addition and during the subsequent 16 hours' stirring after which ammonium chloride (660 g.) was added during 2½ hours and the ammonia evaporated on the steam-bath. Ether (3 l.) was added, and the solid residue obtained on filtering was dissolved in water. A small quantity of tar was removed by filtration, the solution was extracted thoroughly with ether, and the combined ethereal solutions were washed with dilute sulphuric acid and water and then dried. Evaporation of the solvent and distillation gave pent-2-en-4-yn-1-ol (201 g.), b. p. 71–73°/19 mm., n_D^{20} 1.4972. Light absorption: Maximum, 2230 Å.; ϵ = 15,000. Infrared, 2290 Å.; ϵ = 10,000 (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77, give b. p. 90°/50 mm., n_D^{20} 1.4933; maximum, 2230 Å.; ϵ = 14,000). The α -naphthylurethane had m. p. 111–112°, undepressed on admixture with an authentic specimen (m. p. 110–111°).

(b) The method described above using epibromohydrin (137 g.) and sodium (46 g.) in liquid ammonia (1.2 l.) gave: (i) Pent-2-en-4-yn-1-ol (21 g.), b. p. 80–81°/27 mm., n_D^{20} 1.4963, and (ii) a colourless liquid (10.6 g.), b. p. 74–75°/1.5 mm., n_D^{20} 1.4831, analysing for $C_{10}H_{14}O_2$ (Found: C, 66.75, 66.4; H, 6.7, 6.7. $C_{10}H_{14}O_2$ requires C, 66.65; H, 6.7%). Light absorption: Maximum, 2230 Å.; ϵ = 16,000. Inflexion, 2310 Å.; ϵ = 12,500. The structure of this product has not yet been ascertained.

Hex-3-en-5-yn-2-ol (V).—The method described above using 1-bromo-2:3-epoxybutane (77.5 g.; Delaby, *Compt. rend.*, 1923, 176, 589) and sodium (24 g.) in liquid ammonia (600 c.c.) gave hex-3-en-5-yn-2-ol (21.3 g.), b. p. 82–84°/32 mm., n_D^{20} 1.4860 (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54, give b. p. 79–81°/30 mm., n_D^{20} 1.4842). The phenylurethane had m. p. 83°, undepressed on admixture with an authentic specimen, m. p. 83–84° (Jones and McCombie, *J.*, 1943, 261). The α -naphthylurethane separated from light petroleum (b. p. 60–80°) in clusters of needles, m. p. 83–84°, undepressed on admixture with a specimen prepared from authentic material (Found: N, 5.35. $C_{17}H_{18}O_2N$ requires 5.3%).

As a by-product of this experiment there was obtained a substance (7.5 g.), b. p. 122–124°/32 mm., 66–67°/0.5 mm., n_D^{20} 1.4745, believed to be 2-(2:3-epoxy-1-butoxy)hex-3-en-5-yne, a colourless pleasant-smelling liquid, slowly turning yellow in air (Found: C, 71.85; H, 8.6. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.5%). Light absorption: Maximum, 2230 Å.; ϵ = 13,500. Inflexion, 2280 Å.; ϵ = 12,500. Active hydrogen (Zerewitinoff): The ether (94 mg.) evolved 12.7 c.c. of methane (after heating to 90°) at 20°/772 mm. (0.95 active hydrogen atom). Hydrogenation of the ether (2.06 g.) in ethyl acetate (50 c.c.) in the presence of platinum oxide (10 mg.) (914 c.c. hydrogen absorbed at 13°/760 mm., equivalent to 3.05) gave 2-(2:3-epoxy-1-butoxy)hexane (1.5 g.), b. p. 86–88°/16 mm., n_D^{20} 1.4265 (Found: C, 69.45; H, 12.0. $C_{10}H_{20}O_2$ requires C, 69.7; H, 11.7%). This saturated ether gave a negligible volume of methane in an active hydrogen determination.

Cinnamyl Alcohol.—To sodamide, prepared from sodium (1.75 g.), in liquid ammonia (100 c.c.) was added 1:2-epoxy-3-phenylpropane (10 g.; Levy and Sfras, *Bull. Soc. chim.*, 1931, 49, 1823). After 20 hours' stirring in nitrogen, ammonium chloride (5 g.) was added, and the product was isolated with ether in the usual way. Distillation gave cinnamyl alcohol (7.8 g.), b. p. 85–87°/0.05 mm., n_D^{20} 1.5852, which rapidly solidified. After one crystallisation from ether-pentane it had m. p. 33°, not depressed on admixture with an authentic specimen (m. p. 33°). Only a 50% yield of the alcohol was obtained when the reaction time was reduced to 6 hours.

5-Phenylpent-2-en-4-yn-1-ol (VII).—To sodamide, prepared from sodium (7.7 g.) in liquid ammonia (400 c.c.) as described above, phenylacetylene (35 g.) was added during 15 minutes. After 1 hour's stirring, epichlorohydrin (30.6 g.) was run in during 15 minutes, the solution was stirred for a further 16 hours, and was then worked up in the usual manner. Distillation gave, besides some starting material, two fractions: (i) B. p. 70–72°/1 mm., n_D^{20} 1.5459 (1.8 g.); (ii) *5-phenylpent-2-en-4-yn-1-ol* (6.8 g.) as a pale yellow oil, turning dark yellow on keeping, b. p. 94–96°/10⁻³ mm., n_D^{20} 1.6173 (Found: C, 83.0; H, 6.45. $C_{11}H_{14}O$ requires C, 83.5; H, 6.35%). There was a considerable resinous residue. Light absorption: Maxima, 2590, 2720, 2890 Å.; ϵ = 19,000, 26,000, and 21,000 respectively. The α -naphthylurethane separated from petroleum (b. p. 80–100°) in plates, m. p. 132° (Found: N, 4.25. $C_{23}H_{17}O_2N$ requires N, 4.3%).

5-Phenylpentan-1-ol and 8-Phenylvaleric Acid.—A solution of the above carbinol (1 g.) in ethyl acetate (30 c.c.) was shaken with hydrogen in the presence of platinum oxide (10 mg.) until absorption was complete. Removal of catalyst and solvent, gave on distillation *5-phenylpentan-1-ol* (0.75 g.), b. p. 150–151°/18 mm., n_D^{20} 1.5170 (v. Braun, *Ber.*, 1911, 44, 2867, gives b. p. 155°/20 mm.). Oxidation of the saturated carbinol (0.6 g.) with chromic acid in the usual way gave *8-phenylvaleric acid* (0.4 g.) which after crystallisation from water had m. p. 57.5° (Staudinger and Müller, *Ber.*, 1923, 56, 713, give m. p. 57°).

Non-2-en-4-yn-1-ol (VIII).—1-Hexyne (80 g.) was caused to react with sodamide, made from sodium (23.5 g.) in liquid ammonia (1 l.), as previously described, but instead of being cooled, the reaction flask was well lagged with cork dust. Epichlorohydrin (80 g.) was dropped in during 1 hour, then the solution was stirred for 42 hours without cooling, the volume being kept constant by adding more liquid ammonia occasionally. On working up in the usual manner, distilling off starting materials, and carefully fractionating the residue through a Widmer column, there was obtained *non-2-en-4-yn-1-ol* (24 g.) as a pleasant-smelling colourless oil, b. p. 67°/0.1 mm., n_D^{20} 1.4920 (Found: C, 77.5; H, 10.5. $C_9H_{14}O$ requires C, 78.2; H, 10.2%). Light absorption: Maxima, 2280, 2370 Å.; ϵ = 14,000 and 12,000 respectively. The α -naphthylurethane separated from light petroleum (b. p. 40–60°) as a microcrystalline powder, m. p. 69° (Found: N, 4.75. $C_{20}H_{14}O_2N$ requires N, 4.55%). In an experiment in which exactly the same conditions were employed as for the condensation with sodium acetylide (*viz.*, hexyne: epichlorohydrin = 2:1, reaction time 20 hours, cooling in alcohol-carbon dioxide), no appreciable amount of non-2-en-4-yn-1-ol could be detected.

n-Nonyl Alcohol.—Non-2-en-4-yn-1-ol (1.08 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen with platinum oxide until absorption was complete. Removal of catalyst and solvent gave *n-nonyl alcohol* (0.8 g.), b. p. 115°/22 mm., n_D^{20} 1.4355; the *p*-nitrophenylurethane had m. p. 106°; the α -naphthylurethane had m. p. 64° (Ellis and Reid, *J. Amer. Chem. Soc.*, 1932, 54, 1674, give b. p. 213.5°, n_D^{20} 1.4320. Hoppenbrouwers, *Rec. Trav. chim.*, 1932, 51, 951, gives m. p. 104° for the *p*-nitrophenylurethane. Adamson and Kenner, *J.*, 1934, 838, give m. p. 65.5° for the α -naphthylurethane.)

The authors thank the Rockefeller Foundation for financial assistance and the University of London for Post-graduate studentships (L. J. H. and F. S.). They are indebted to Dr. E. A. Braude for the light-absorption data.

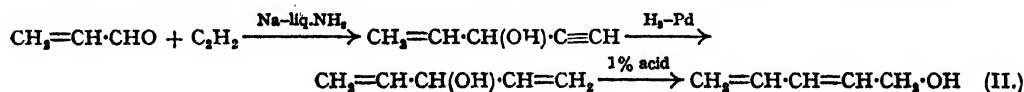
315. Researches on Acetylenic Compounds. Part XIV. A Study of the Reactions of the Readily Available Ethynyl-ethylenic Alcohol, Pent-2-en-4-yn-1-ol.

By SIR IAN HEILBRON, E. R. H. JONES, and F. SONDHEIMER.

A variety of reactions of pentenynol, illustrated in the accompanying diagram, has been studied. These include partial hydrogenation, carboxylation, hydration to methylfuran, condensation with formaldehyde to the C_8 glycol, oxidative coupling to the C_{10} glycol, and oxidation to the corresponding carboxylic acid with chromic acid. Light-absorption data for the diacetylene system in extended chromophores are quoted and discussed.

THE route hitherto available (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77) to the ethynylethylenic alcohol, pent-2-en-4-yn-1-ol (I), was extremely unsatisfactory, only about a 4% yield based on acraldehyde being achieved. Now that this interesting substance can be obtained in quantity in a single-stage preparation from easily available starting materials, as described in the preceding paper, a study of some of its many reaction possibilities became worth while.

In the first place its partial hydrogenation to pentadienol (II) was investigated. This substance, which had been found to give an elastic polymer, had previously been prepared (Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84) in only very poor yield (*ca.* 5% based on acraldehyde) by the route indicated in the accompanying formulæ. A direct preparation from pentenynol (I) offered the possibility of obtaining reasonable samples of this material



for more detailed polymerisation studies. Partial hydrogenation using a palladium-calcium carbonate catalyst proceeded in a manner similar to that already observed (Heilbron, Jones, McCombie, and Weedon, *loc. cit.*) with the homologous hexenynol, and after careful fractionation a 50% yield of the dienol (II) was obtained.

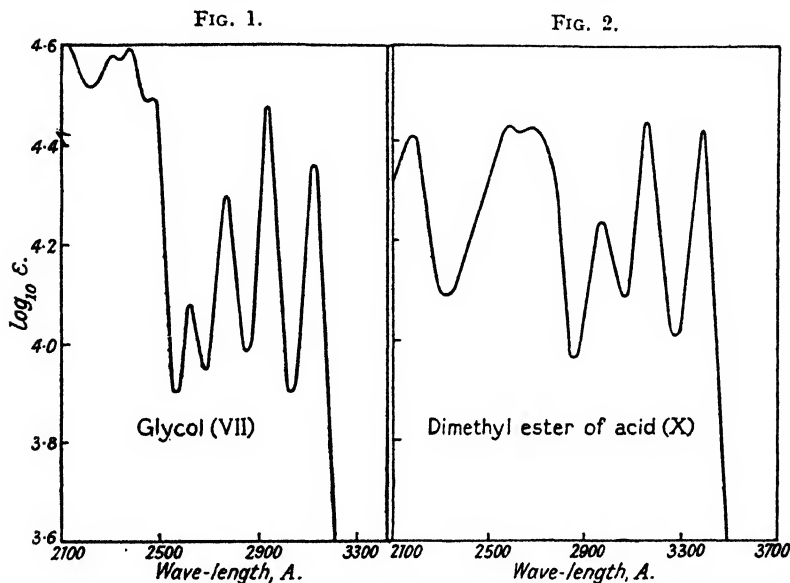
Carboxylation of the Grignard complex (*cf.* Haynes and Jones, *J.*, 1946, 503) gave the *hydroxy-acid* (III), exhibiting the expected light-absorption properties and converted into ϵ -hydroxyhexoic acid on complete hydrogenation. Hydration of pentenynol with sulphuric acid and mercuric sulphate proceeded analogously to that of the homologous hexenynol (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54) and yielded 35% of 2-methylfuran (IV); the yield of this highly volatile material could almost certainly be improved by more detailed attention to the reaction conditions, etc.

When pentenynol was originally obtained (*J.*, 1945, 77) one of the few reactions carried out with it involved the condensation of its Grignard complex with butaldehyde to give an ethylenic-acetylenic glycol. Attempts to condense formaldehyde with pentenynol in the same manner were not successful, but by using a copper hydroxide catalyst (General Aniline and Film Corp., U.S.P. 2,238,471) and an aqueous solution of formaldehyde, the *diol* (V) was obtained in 40% yield. Its light-absorption properties were as expected for the structure (V) and this was conclusively proved by hydrogenation to hexane-1:6-diol. The Mannich condensation of pentenynol with formaldehyde and diethylamine, to give the amino-alcohol (VI), has already been described in Part XI (p. 1578).

In Part XII of this series (p. 1580), in which the scope of the oxidative coupling of ethynyl-carbinols to diacetylenic glycols in the presence of cuprous ammonium chloride has been considerably extended, the employment of the ethynyl-ethylenic alcohol, hex-3-en-5-yn-2-ol, in such reactions was described. Pentenynol also can readily be oxidised by air in cuprous salt solution giving a good yield of the *glycol* (VII), hydrogenated to decane-1:10-diol. The light-absorption curve for this glycol is given in Fig. 1, and in the Table the data are compared with those for its homologue, the preparation of which from hexenynol is described in Part XII. It will be noted that the locations of the longer wave-length bands (2930 and 3120 Å.) of both glycols approximate very closely to those recorded for decatetraenol, containing four conjugated ethylenic linkages. Therefore, although conjugated diacetylenes, unlike the vinyl-acetylenes and dienes, fail to show high intensity absorption in the ultra-violet (see Part XII), when the diacetylene grouping becomes part of a larger chromophore, as in glycols such as (VII), it appears to be capable of transmitting electronic vibrations, giving rise to absorption

corresponding to fully conjugated systems. As in all other cases where acetylenic bonds are involved in chromophoric systems, considerable intensity reductions are observed. The multiplicity of shorter wave-length bands indicates a marked tendency of the diacetylene grouping to participate in partial chromophores, probably of the en-yne and ene-diyne types.

Oxidation of pentenynol in acetone solution with chromic acid (cf. Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) gives a 60% yield of the corresponding acid (VIII) which,



	$\gamma_{\max.}, \text{\AA.}$	$\epsilon_{\max.}$		$\gamma_{\max.}, \text{\AA.}$	$\epsilon_{\max.}$
Deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (VII)	2300	38,000	Pent-3-en-1-yn-5-ol-1-carboxylic acid (III)	2450	13,000
	2370	39,000			
	2470	30,000	But-1-en-3-yne-1-carboxylic acid (VIII)	2420	12,500
	2620	12,000			
	2765	20,000	Methyl ester of (VIII)	2440	18,000
	2930	30,000		* 2510	15,500
	3120	23,000			
Dodeca-3 : 9-diene-5 : 7-diyne-2 : 11-diol ¹	2350	42,000	Hex-3-en-1-yn-5-ol-1-carboxylic acid ²	2455	12,000
	2470	30,500		* 2560	9,500
	2640	10,500	Sorbic acid	2540	25,000
	2770	18,000			
	2930	30,500	Dimethyl ester of (X)	2190	26,000
	3120	24,500		2580	27,500
Decatetraenol ²	2985	64,000		2680	27,500
	3110	64,000		2970	17,500
				3160	28,500
				3390	27,500

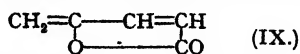
* Inflexion.

¹ For preparation see Part XII, p. 1579.

² Reichstein and Trivelli, *Helv. Chim. Acta*, 1932, 15, 1074.

³ Haynes and Jones, *J.*, 1946, 503.

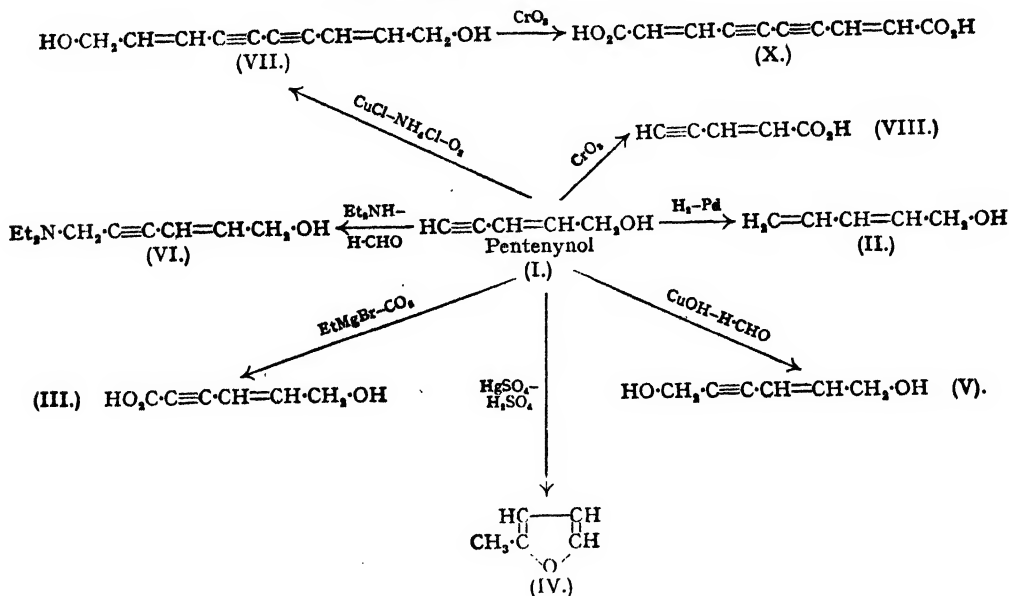
though stable in ether solution, rapidly polymerises when pure even in a vacuum in the dark. This instability may be due to the facile occurrence of an intramolecular hydration, leading to



the formation of the unsaturated lactone (IX), which would be expected to polymerise easily. Such a hypothesis is all the more convincing, since the *methyl* ester is comparatively stable. The structure of the acid is confirmed by hydrogenation to valeric acid and by the light-absorption data for the acid and its ester (Table) which are somewhat similar (although, of

course, lower in intensity) to that of sorbic acid. The glycol (VII) when oxidised under similar conditions with chromic acid gives the amorphous *di-acid* (X) purified through its crystalline *dimethyl ester*, proof of structure being obtained by hydrogenation to sebacic acid. Light-absorption data for the ester (see Fig. 2 and Table) again indicate the participation of the diacetylene group in an extended conjugated system.

Reactions of Pent-2-en-4-yn-1-ol.



EXPERIMENTAL.

(Light-absorption data determined in alcohol solutions.)

Penta-2:4-dien-1-ol (II).—A solution of pent-2-en-4-yn-1-ol (160 g.) in ethyl acetate (400 c.c.) was hydrogenated using a palladium–calcium carbonate catalyst (20 g.; 0.3% Pd) until 46.7 l. of gas had been absorbed. The product obtained after removal of catalyst and solvent was carefully fractionated through a column containing a 50 × 1.5 cm. section packed with single turn glass helices. The numerous fractions collected were divided into two portions: (i) B. p. 32–34°/1.5 mm. (34 g.), n_D^{18} 1.4620–1.4730. (ii) *Penta-2:4-dien-1-ol* (82.5 g.), b. p. 34–40°/1.5 mm., n_D^{18} 1.4770–1.4893. There was a considerable resinous residue. Light absorption: Maximum, 2230 Å., ϵ = 26,000. (Heilbron *et al.*, *J.*, 1945, 87, give b. p. 95–97°/100 mm., n_D^{18} 1.4902. Maximum, 2230 Å., ϵ = 25,000.) The various fractions composing portion (ii) differed but slightly in their light-absorption intensities; the refractive index variations are doubtless due to the presence of geometrical isomerides.

A warm solution of the pentadienol (0.4 g.) and maleic anhydride (0.5 g.) in benzene (4 c.c.) was set aside at 20° overnight. Recrystallisation of the separated solid from water gave the lactonic acid (0.48 g.), m. p. 176° (Heilbron *et al.*, *loc. cit.*, give m. p. 175–176°) undepressed on admixture with an authentic specimen.

Pent-3-en-1-yn-5-ol-1-carboxylic Acid (III).—Benzene (200 c.c.) was gradually added to a solution of ethylmagnesium bromide (from 12.5 g. magnesium) in ether (250 c.c.) at the same time as the latter was distilled off. When the temperature of the issuing vapours reached 70°, the mixture was cooled (ice) and pent-2-en-4-yn-1-ol (20.5 g.) was added during $\frac{1}{2}$ hour. After refluxing for $1\frac{1}{2}$ hours, the suspension of a fine white powder was shaken in an autoclave with solid carbon dioxide (500 g.) for 22 hours at 20°. The complex was decomposed with ice and dilute sulphuric acid and the aqueous layer was continuously extracted with ether during 24 hours. The combined extracts were washed with sodium bicarbonate solution, and from the ether layer pent-2-en-4-yn-1-ol (12.8 g.) was recovered. The bicarbonate extract was acidified and continuously extracted with ether for 48 hours. The product so obtained was crystallised from benzene–ethyl acetate (4:1) giving the *acid* (6.2 g.) as a micro-crystalline powder, m. p. 135–136°, which after subliming at 90° (bath temp.)/10^{–4} mm. and crystallisation from the same solvents formed plates, m. p. 137° (Found: C, 57.3; H, 5.05. $\text{C}_8\text{H}_8\text{O}_2$ requires C, 57.15; H, 4.8%). The *S-benzylisothiuronium* salt separated from ethyl acetate–ethanol (4:1) in plates, m. p. 155–156° (decomp.) (Found: N, 9.55. $\text{C}_{14}\text{H}_{18}\text{O}_2\text{N}_2\text{S}$ requires N, 9.6%).

A solution of the acid (1.9 g.) in methanol (30 c.c.) was hydrogenated using platinum oxide (10 mg.) as catalyst. The crude ϵ -hydroxyhexoic acid (1.8 g.) was converted into the lactone by heating it at 160° for 5 minutes, and the lactone was then heated for 3 hours with hydrazine hydrate on the steam-

bath. The hydrazide of α -hydroxyhexoic acid crystallised from ethyl acetate-methanol (6:1) in plates, m. p. 115° (Natta, Hill, and Carothers, *J. Amer. Chem. Soc.*, 1934, **56**, 456, give m. p. 114–115°).

2-Methylfuran (IV).—A mixture of pent-2-en-4-yn-1-ol (8 g.), sulphuric acid (40 c.c., 0.5% w/v), and mercuric sulphate (0.2 g.) was distilled in steam until the distillate was no longer cloudy (about 50 c.c. in $\frac{1}{2}$ hour). The distillate was saturated with salt, the upper layer separated and dried (CaCl_2), and distillation gave 2-methylfuran (2.6 g.), b. p. 64°/769 mm., n_D^{20} 1.4342 (Kizhner, *J. Gen. Chem. Russia*, 1931, **1**, 1212, gives b. p. 64°/749 mm., n_D^{20} 1.4365).

The furan (0.25 g.) was added to a warm solution of maleic anhydride (0.3 g.) in benzene (1 c.c.). After $\frac{1}{2}$ hour, the solvent was evaporated, and the residue was recrystallised from ether to give the adduct (0.4 g.) as needles, m. p. 81° (Rinckes, *Rec. Trav. chim.*, 1931, **50**, 1127, gives m. p. 80°).

Hex-2-en-4-yne-1:6-diol (V).—A copper hydroxide catalyst was made by precipitating a solution of cuprous chloride (3 g.) in hydrochloric acid (45 c.c., 12%) with potassium hydroxide solution (45 c.c., 40%); it was filtered off and washed well with water. The wet catalyst was then stirred with pent-2-en-4-yn-1-ol (15 g.), formaldehyde solution (20 g.; 40% w/v), water (6 c.c.), and calcium carbonate (0.2 g.) under reflux for 42 hours at 90° in nitrogen. The catalyst was filtered off, and distillation gave some starting material (2 g.) and a viscous liquid (7.9 g.), b. p. 120–130°/10⁻³ mm., n_D^{20} 1.5442. This rapidly solidified and after crystallisation from benzene-ethyl acetate (6:1) furnished the glycol (6.8 g.) as needles, m. p. 58–59° (Found: C, 64.1; H, 6.9. $\text{C}_8\text{H}_{12}\text{O}_4$ requires C, 64.25; H, 7.2%). Light absorption: Maximum, 2270 Å.; ϵ = 15,000. Inflection, 2370 Å.; ϵ = 12,000. The bisphenylurethane crystallised from ethanol in needles, m. p. 157° (Found: N, 8.0. $\text{C}_{20}\text{H}_{18}\text{O}_4\text{N}_2$ requires N, 8.0%).

Hexane-1:6-diol.—A solution of the above glycol (1 g.) in methanol (40 c.c.) was hydrogenated using platonic oxide catalyst (10 mg.). The product distilled at 147–148°/18 mm. as a viscous oil which rapidly solidified, and crystallisation from ether gave hexane-1:6-diol (0.6 g.), m. p. 41–42° (Hamonet, *Bull. Soc. chim.*, 1905, **33**, 539, gives b. p. 152°/17 mm., m. p. 42°). The bisphenylurethane formed needles, m. p. 170°, from ethanol (Hamonet, *loc. cit.*, gives m. p. 171–172°).

Deca-2:8-diene-4:6-diyne-1:10-diol (VII).—Pent-2-en-4-yn-1-ol (34 g.) was added during 10 minutes to a stirred solution of ammonium chloride (240 g.) and cuprous chloride (150 g.) in water (600 c.c.) at 55°. Air was then bubbled through the red solution (at 55°) for 2½ hours, and the product was isolated by repeated ethereal extraction. Crystallisation from water gave the diol (22 g.) as yellow plates, sintering at 130°, m. p. 153–155° (decomp.) which, on further crystallisation from the same solvent or from benzene (in an atmosphere of nitrogen), formed colourless plates, m. p. 155–156° (decomp.) (Found: C, 74.25; H, 6.05. $\text{C}_{10}\text{H}_{16}\text{O}_4$ requires C, 74.05; H, 6.2%). The glycol develops a brown colour in air or light. The dibenzoate, prepared with benzoyl chloride in pyridine at 20° overnight, separated from light petroleum (b. p. 80–100°) in needles, m. p. 96° (Found: C, 77.4; H, 5.0. $\text{C}_{24}\text{H}_{28}\text{O}_6$ requires C, 77.8; H, 4.9%). Light absorption: Maxima, 2340, 2640, 2810, 2950, 3150 Å.; ϵ = 63,000, 12,000, 22,000, 26,000, and 23,500 respectively.

In smaller scale experiments, in which the proportion of copper salt to carbinol was increased still further, yields up to 72% were obtained.

Hydrogenation of the glycol (0.49 g.) in methanol (40 c.c.) with platonic oxide (5 mg.) and crystallisation of the product from benzene gave decane-1:10-diol (0.31 g.) as a microcrystalline powder, m. p. 71–71.5° (Folkers and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 1146, give m. p. 70.8–71.8°; Manske, *Org. Synth.*, Coll. Vol. II, 154, gives m. p. 72–74°).

But-1-en-3-yne-1-carboxylic Acid (VIII).—A mixture of chromium trioxide (35 g.) and concentrated sulphuric acid (56 g.) was made up to 175 c.c. with water, and this solution was added, with constant shaking during 30 minutes, to a cooled solution of pent-2-en-4-yn-1-ol (20.5 g.) in acetone (150 c.c.), the temperature being kept at 15°. After being shaken for a further 1½ hours, the mixture was poured into water and repeatedly extracted with ether. The acidic material was removed by extraction with sodium bicarbonate solution, which after acidification and ether extraction furnished but-1-en-3-yne-1-carboxylic acid (14.1 g.) as a light yellow crystalline mass, m. p. 92–93°; crystallisation from light petroleum (b. p. 80–100°) gave long colourless needles, m. p. 94°. The acid soon forms an acetone insoluble polymer, even when sealed up in a vacuum in the dark (Found: C, 62.55; H, 4.5. $\text{C}_6\text{H}_6\text{O}_2$ requires C, 62.5; H, 4.2%). The S-benzylisothiuronium salt separated from ethyl acetate in plates, m. p. 172–173° (Found: N, 10.9. $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}_2\text{S}$ requires N, 10.7%). The acid (10 g.) was refluxed for 16 hours with methyl-alcoholic sulphuric acid (2%; 200 c.c.); isolation by the usual procedure gave, besides some high boiling material, methyl but-1-en-3-yne-1-carboxylate (5.35 g.) as a pleasant smelling oil, b. p. 59°/34 mm., n_D^{20} 1.4820. On ice cooling it solidified to plates, m. p. 19–20° (Found: C, 65.7; H, 5.85. $\text{C}_6\text{H}_6\text{O}_2$ requires C, 65.45; H, 5.5%). A solution of the acid (0.65 g.) in ethyl acetate (30 c.c.) was shaken with hydrogen in the presence of platonic oxide until absorption was complete. The crude valeric acid (0.6 g.) was converted into the amide in the usual way, to give the latter as leaflets, m. p. 104–105° (Robertson, *J.*, 1919, 1220, gives m. p. 106°).

Octa-1:7-diene-3:5-diyne-1:8-dicarboxylic Acid (X).—A mixture of chromium trioxide (13 g.) and concentrated sulphuric acid (20.8 g.) was made up to 65 c.c. with water, and this solution was added, with constant shaking, to a cooled solution of deca-2:8-dien-4:6-diyne-1:10-diol (4 g.) in acetone (75 c.c.) at such a rate as to keep the temperature at 25°. The solution was shaken for a further hour, then poured into water and repeatedly extracted with ether. The acidic material was removed by shaking with sodium bicarbonate solution, which after acidification and ether extraction gave octa-1:7-dien-3:5-diyne-1:8-dicarboxylic acid (1.7 g.) as a yellow amorphous powder, charring at ca. 300°, which after several precipitations from aqueous methyl alcohol was pale yellow but still non-crystalline.

The diacid (1.6 g.) was refluxed with methyl-alcoholic sulphuric acid (1.5%; 70 c.c.) for 14 hours. On cooling, a mass of straw-coloured plates separated, and were filtered off; the filtrate was poured into water, and excess of sodium bicarbonate solution was added. Ether extraction and crystallisation of the resulting solid from methyl alcohol gave, when mixed with the solid obtained before, dimethyl octa-1:7-dien-3:5-diyne-1:8-dicarboxylate (1.35 g.) as straw-coloured plates, m. p. 103–104°. On

further recrystallisation from the same solvent, it was obtained as light yellow plates, m. p. 106° , which gradually develop a brown colour (Found: C, 66.3; H, 4.7. $C_{13}H_{10}O_4$ requires C, 66.05; H, 4.65%).

The diacid was regenerated by keeping a solution of the ester (0.3 g.) in methyl alcohol (125 c.c.) containing potassium hydroxide (4 g.) for 48 hours at room temperature. Most of the solvent was evaporated, water was added, and the acid product, isolated from the acidified reaction mixture with ether, gave the diacid (0.21 g.) having the same properties as before (Found: C, 63.85, 63.6; H, 3.9, 4.05. $C_{10}H_8O_4$ requires C, 63.15; H, 3.2%). Light absorption: Maxima, 2580, 2650, 2955, 3155, 3375 μ ; $\epsilon = 28,500, 28,500, 17,500, 28,500$, and $28,500$ respectively.

Sebacic Acid.—The di-ester (130 mg.) in methyl alcohol (75 c.c.) was shaken with hydrogen in the presence of platinum oxide (10 mg.) until absorption was complete. The solution was refluxed for $1\frac{1}{2}$ hours with potassium hydroxide (2 g.), and working up in the usual way gave sebacic acid (70 mg.), m. p. 132° , undepressed on admixture with an authentic specimen (m. p. $131-132^{\circ}$).

The authors thank the Rockefeller Foundation for financial assistance, and one of them (F. S.) is indebted to the University of London for a Post-graduate Studentship. Light-absorption data were determined by Dr. E. A. Braude.

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[Received, January 18th, 1947.]

316. Some Organic Derivatives of Hexachlorodisiloxane.

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Methyl, ethyl, and phenyl derivatives of hexachlorodisiloxane have been prepared by reaction of the oxychloride with the corresponding Grignard reagent in ethereal solution. Hydrolysis of monochloropentaethylidisiloxane gave a stable monomeric hydroxy-compound.

DESPITE the preparation of a large number of organic monosilicon chlorides by Kipping and his co-workers and others, no attempt has been made to prepare organic silicon oxychlorides. In view of the predominance of the Si-O-Si linkage in the "silicone" polymers, it was of interest to prepare certain simple organic silicon oxychlorides and to examine their properties. In this paper the reactions between hexachlorodisiloxane, the simplest silicon oxychloride known, and methylmagnesium chloride and ethyl- and phenyl-magnesium bromides are described. The mono-, di-, tri-, tetra-, and penta-ethyl and the dimethyl and diphenyl derivatives of the oxychloride have been isolated.

All the organodisiloxane *chlorides* isolated were colourless mobile liquids with melting points below room temperature, which hydrolysed readily with water. The products of hydrolysis from Si_2OCl_2Et , $Si_2OCl_2Et_2$, $Si_2OCl_2Me_2$, and $Si_2OCl_2Ph_2$ were white solids, whilst $Si_2OCl_2Et_3$ gave a translucent viscous liquid, which polymerised further on standing to a rubber-like solid. The products obtained by the hydrolysis of $Si_2OCl_2Et_4$ and Si_2OClEt_5 were liquids which were readily soluble in ether. From the products of hydrolysis of Si_2OClEt_5 it was possible to isolate in theoretical yield a monohydroxy-derivative, which was a stable liquid with a smell reminiscent of that of camphor. These hydrolysis experiments, which were qualitative, indicated a small decrease in the ease of hydrolysis as the number of substituent organic groups was increased.

The action upon diethyltetrachlorodisiloxane of ammonium fluoride or potassium hydrogen difluoride led to formation of ethylsilicon trifluoride, which was fully characterised, together with a residue of polymerised material. This result, which illustrates the instability of the Si-O-Si bond to fluorination, is in agreement with recent work by Booth and Osten (*J. Amer. Chem. Soc.*, 1945, **67**, 1092), who obtained a large yield of silicon tetrafluoride in the reaction between hexachlorodisiloxane and antimony trifluoride. The same point has been demonstrated by Emeléus and Wilkins, who prepared ethylsilicon trifluoride by the action of sulphuric acid on a mixture of ethylsilicic acid and calcium fluoride (*J.*, 1944, 454). Experiments on the fluorination of the other alkyl and aryl derivatives described in this paper have not so far been made, but some at least might be expected to yield stable fluoro-derivatives.

The photochemical chlorination of tetrachlorodiethylidisiloxane gave a theoretical yield of the fully chlorinated derivative. Thermal chlorination of the same compound at $150-200^{\circ}$ resulted in the formation of a small quantity of hexachloroethane, indicating that some fission of the Si-C bond had occurred. The action of alkali on the fully chlorinated material from the photochemical reaction leads to fission of the C-Si bond and the subsequent formation of tetrachloroethylene, obtained from the initial hydrolysis product, pentachloroethane, by loss of hydrogen chloride. This is in agreement with the known reaction of chloroalkylmonosilicon chlorides with alkali.

Structural isomerism should be possible in the di-, tri-, and tetra-substituted derivatives of

hexachlorodisiloxane. This point has not been fully studied, but in the case of the diethyl derivative; $\text{Si}_2\text{OCl}_4\text{Et}_2$, the action of ammonium fluoride yields only ethylsilicon trifluoride, which indicates that one ethyl group is attached to each silicon atom. No fission of the C-Si bond was observed during this reaction. The preparation of hexa-alkyl- and -aryl-disiloxanes was attempted by Schumb, Ackerman, and Saffer (*J. Amer. Chem. Soc.*, 1938, **60**, 2486) by applying the Wurtz reaction to hexachlorodisiloxane and the alkyl or aryl halides. These experiments yielded, however, only the fully substituted monosilicon derivatives in good yield. Using the Grignard reaction with phenylmagnesium bromide, Schumb and Saffer (*ibid.*, 1939, **61**, 363) obtained a 40% yield of hexaphenyldisiloxane. The corresponding reaction using hexabromodisiloxane yielded small amounts of the monosilicon derivative, triphenylsiliconal. In the experiments described here no products of low molecular weight corresponding to monosilicon derivatives were detected. Yields of the desired products were relatively high, but in every case a residue consisting of material of high molecular weight was obtained.

EXPERIMENTAL.

Analysis.—The determination of the percentage of chlorine and silicon present in the compounds obtained was carried out by Gillian, Liebhopsky, and Wimslow's method (*J. Amer. Chem. Soc.*, 1941, **63**, 801). Owing to the low volatility of the derivatives of Si_2OCl_4 it was possible to weigh the sample out in a small gelatin ampoule and then to bring it into reaction with A.R. sodium peroxide in a Parr microbomb. The quantity of sample weighed out varied with the percentage of chlorine in the compounds under analysis, from about 90 mg. of $\text{Si}_2\text{OCl}_4\text{Et}$ to about 150 mg. of $\text{Si}_2\text{OCl}_4\text{Et}_2$.

Hexachlorodisiloxane.—Four methods were investigated for this preparation: (i) the reaction between a chlorine-oxygen mixture and elemental silicon at temperatures between 700° and 800°; (ii) the reaction between silicon tetrachloride and oxygen at 900–950°; (iii) the oxidation of silicochloroform by means of solid oxidising agents at temperatures from 200° to 400°; (iv) the partial hydrolysis of silicon tetrachloride in ethereal solution. Method (iii) resulted mainly in the complete oxidation of the silico-chloroform, leading to formation of silicon and hydrogen chloride. Small yields of Si_2OCl_4 were obtained by method (iv), but the main portion of the products consisted of higher oxychlorides. Methods (i) and (ii) gave results which were suitable for the preparation of Si_2OCl_4 in large quantities. The reaction between silicon tetrachloride and oxygen had the additional merit of being capable of adaptation for use as a continuous process. Dry oxygen was passed at the rate of 2–4 l./hr. through silicon tetrachloride kept about 10° below its b. p. The mixture of silicon tetrachloride and oxygen thus produced passed through the furnace tube maintained at 900–950°. The products together with excess of silicon tetrachloride were condensed by means of two water-cooled, double-surface condensers, and the condensed liquid was returned to the silicon tetrachloride boiler. The b. p. of the silicon tetrachloride increased as the experiment proceeded, and after 2–5 days the apparatus was shut down and the silicon tetrachloride fractionated. Hexachlorodisiloxane, b. p. 137–138°, was collected. A small residue of higher oxychlorides was obtained.

The Reaction of Hexachlorodisiloxane with a Grignard Reagent.—In all the experiments the same general method was employed. Variations in the reaction conditions are noted in the separate details of each experiment. The Grignard reagent was prepared from the organic halide by the usual method. A solution of the chloro-compound in anhydrous ether was placed in a three-necked flask (1 g.-mol. of Si_2OCl_4 being dissolved in approx. 1 l. of ether), fitted with a stirrer, a spiral double-surface condenser, and tap-funnel. The Grignard solution was filtered through glass-wool into the tap-funnel to remove excess of magnesium, and then run slowly into the well-stirred solution of the halide. Precipitation of magnesium chlorobromide began at once. When the addition was complete, the solution was refluxed for 3–6 hours to ensure completion of the reaction. The reaction mixture was allowed to cool, and the chlorobromide filtered off rapidly through a large Büchner funnel. The residue on the filter was well washed with anhydrous ether. Removal of the ether was carried out by distillation, and the residue was then fractionated. Arrangements were made, by means of drying tubes containing silica gel, to exclude moisture from the reaction vessel, distillation columns, and other apparatus in which the halides were handled. All apparatus was thoroughly dried before use.

Monoethylpentachlorodisiloxane.—116 G. (0.875 g.-mol.) of ethylmagnesium bromide were treated with 200 g. (0.7 g.-mol.) of Si_2OCl_4 . The products after separation were fractionated several times under reduced pressure, a 13" column packed with Fenske spirals being used. 47 G. (0.17 g.-mol.) of pure monoethylpentachlorodisiloxane were obtained (b. p. 60.0–61.5°/17 mm., 163–164°/757 mm.); yields, crude 40%, pure 24% (Found: Cl, 63.6; Si, 19.9; C, 8.9; H, 1.9. $\text{Si}_2\text{OCl}_4\text{Et}$ requires Cl, 63.7; Si, 20.1; C, 8.7; H, 1.8%).

Diethyltetrachlorodisiloxane.—333 G. (2.5 g.-mols.) of ethylmagnesium bromide were treated with 285 g. (1 g.-mol.) of Si_2OCl_4 . 236 G. (87%) of crude product were obtained, from which 75 g. (0.28 g.-mol., 28%) of pure diethyltetrachlorodisiloxane were collected (b. p. 72.5°/12 mm., 186–187°/757 mm.) by fractionation under reduced pressure through a modified Widmer column, packed with Monel-metal gauze spirals and utilising a partial condensation vapour take-off head (Found: Cl, 52.3; Si, 20.6; C, 17.9; H, 3.7. $\text{Si}_2\text{OCl}_4\text{Et}_2$ requires Cl, 52.1; Si, 20.6; C, 17.7; H, 3.7%).

Triethyltrichlorodisiloxane.—498 G. (3.75 g.-mols.) of ethylmagnesium bromide were caused to react with 285 g. (1 g.-mol.) of Si_2OCl_4 . 231 G. (85%) of crude product were obtained, from which, by repeated fractionation under reduced pressure by means of the column described in the previous preparation, it was possible to isolate 78 g. (0.295 g.-mol., 29.5%) of pure triethyltrichlorodisiloxane (b. p. 72.5–73.5°/7 mm., 202–203°/757 mm.) (Found: Cl, 40.0; Si, 21.5; C, 26.8; H, 5.7. $\text{Si}_2\text{OCl}_4\text{Et}_3$ requires Cl, 40.0; Si, 21.1; C, 27.1; H, 5.7%).

Tetraethyldichlorodisiloxane.—An attempt to prepare the pentaethylmonochloro-compound by

reaction of 1 g.-mol. of Si_2OCl_4 with 5 g.-mols. of ethylmagnesium bromide led to the isolation of *tetraethyldichlorodisiloxane*. When 6.25 g.-mols. of the Grignard reagent were used, difficulty was experienced in separating the product owing to the bulk of the magnesium chlorobromide, and this bulk of inert product probably accounts for the reaction ceasing at the tetra-substituted stage. 19.4 G. (78%) of crude tetraethyl compound were obtained, which after repeated fractionation gave 29 g. (0.11 g.-mol., 11%) of pure product (b. p. $96-98^\circ/13$ mm., $215-216^\circ/757$ mm.) (Found: Cl, 27.4; Si, 20.9; C, 36.9; H, 7.4. $\text{Si}_2\text{OCl}_2\text{Et}_4$ requires Cl, 27.4; Si, 21.6; C, 37.0; H, 7.8%). 12 G. of a fraction consisting mainly of pentaethyl compound were obtained.

Pentaethylmonochlorodisiloxane.—The preparation of this compound was carried out in two stages. The triethyl compound was first prepared as described above, the crude material being isolated and analysed for replaceable chlorine. An amount of ethylmagnesium bromide (366 g., 2.75 g.-mols.) was prepared sufficient to reduce the content of the replaceable chlorine in 293 g. of triethyl compound to that corresponding to $\text{Si}_2\text{OClEt}_3$, together with the usual 25% excess of Grignard reagent over the halide. Reaction was slower than when the unsubstituted chloride was used and it was necessary to reflux the mixture overnight. 237 G. of crude material were obtained, from which it was possible after repeated fractionations under reduced pressure to obtain 34 g. (0.135 g.-mol., 12.5%) of pure *pentaethyl* compound (b. p. $86-88^\circ/1$ mm., $226-227^\circ/757$ mm.) (Found: Cl, 13.9; C, 48.1; H, 10.5. $\text{Si}_2\text{OClEt}_3$ requires Cl, 14.0; C, 47.5; H, 10.0%).

Dimethyltetrachlorodisiloxane.—17 G. (0.1 g.-mol.) of methylmagnesium iodide and 179 g. (2.4 g.-mols.) of methylmagnesium chloride, prepared according to Schmalfuss (*J. pr. Chem.*, 1924, 108, 88), were treated with 285 g. (1 g.-mol.) of Si_2OCl_4 . Reaction proceeded vigorously and the vessel had to be cooled during the early stages of the preparation. 203 G. of crude material were obtained. By using a 28" column filled with Monel-metal gauze spirals and fitted with a heater jacket and utilising a total condensation partial take-off head, 137 g. (0.56 g.-mol., 56%) of pure *dimethyltetrachlorodisiloxane* were obtained (b. p. $67-69^\circ/57$ mm., $143-144^\circ/757$ mm.) (Found: Cl, 57.5; Si, 23.2; C, 10.2; H, 2.5. $\text{Si}_2\text{OCl}_4\text{Me}_2$ required Cl, 58.1; Si, 23.1; C, 9.9; H, 2.5%). The pure material was colourless but became pink in contact with air.

Diphenyltetrachlorodisiloxane.—520 G. (2.85 g.-mols.) of phenylmagnesium bromide reacted with 285 g. (1 g.-mol.) of Si_2OCl_4 . The crude product was separated from the small quantity of diphenyl obtained by fractionation through a 9' Fenske column, fitted with a heater jacket and utilising a total condensation partial take-off head. Further fractionation using the 28" Monel-gauze spiral column used in the previous preparation led to the isolation of 64 g. (0.175 g.-mol., 17.5%) of pure compound (b. p. $114-116^\circ/<1$ mm., $319-320^\circ/757$ mm.) (Found: Cl, 38.6; Si, 15.1; C, 39.2; H, 2.6. $\text{Si}_2\text{OCl}_4\text{Ph}_2$ requires Cl, 38.5; Si, 15.2; C, 39.2; H, 2.7%). The pure material was colourless but on storage became pale yellow.

Pentaethyldisiloxanol.—3 G. of pentaethylchlorodisiloxane were dissolved in 15 ml. of ether and a solution containing 2 g. of sodium hydrogen carbonate dissolved in 10 ml. of water added. A steady evolution of carbon dioxide occurred for 2 hours. The solution was refluxed for a further 3 hours until the evolution ceased. The solution was extracted with portions of ether, the resulting ethereal solution was separated and dried (CaCl_2) overnight. The ether was removed by distillation, and the product distilled under reduced pressure. 2.5 G. (100%) of the *siloxanol* were obtained (b. p. $96-98^\circ/<1$ mm.) [Found: C, 51.4; H, 11.1; *M* (Rast), 215. $\text{Si}_2\text{OEt}_4\text{OH}$ requires C, 51.3; H, 11.1% *M*, 232].

Photochemical Chlorination of Diethyltetrachlorodisiloxane.—Dry chlorine was passed into 32.2 g. of the disiloxane contained in a quartz test-tube irradiated by U.V. light from a mercury-vapour lamp. After 66 hours the increase in weight was 40.5 g. [Calc. for formation of $\text{Si}_2\text{OCl}_4(\text{C}_2\text{Cl}_5)_2$: 40.8 g.]. The bulk of the *bispentachloroethyltetrachlorodisiloxane* distilled within the range $178-183^\circ/<1$ mm. and consisted of a colourless viscous liquid with a faint smell [Found: Cl, 81.1; *M* (Rast), ~650. $\text{C}_4\text{OCl}_4\text{Si}_2$ requires Cl, 80.6%; *M*, 617].

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for a grant in aid of this research.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

[Received, January 23rd, 1947.]

317. Alkyl, Aryl, and Alkoxy-derivatives of Silicon Tetrachloride and Silicochloroform.

By H. J. EMELÉUS and S. R. ROBINSON.

The compounds *ethyldichlorosilane*, *diethylchlorosilane*, *phenyldichlorosilane*, *diphenylchlorosilane*, *benzyldichlorosilane*, and *dibenzylchlorosilane* have been prepared from silicochloroform by the Grignard reaction. A new method for the preparation of alkyl-alkoxysilanes by the reaction between sodium alkoxide and an alkyl silicon chloride is reported. *Diethyldimethoxysilane* is described. Other known compounds of this type were prepared by the same method and characterised.

THE alkyl, aryl, and alkoxy-derivatives of silicochloroform and silicon tetrachloride are of importance because on hydrolysis they give materials which are known to form resins when heated. The preparation of these resin intermediates from silicochloroform is in fact a useful alternative to their preparation by hydrolysis of the corresponding derivatives of silicon tetrachloride. The only reference in the literature to compounds of the type SiRHX_3 , where X

is a halogen atom, is in work by Rochow (*J. Amer. Chem. Soc.*, 1945, **67**, 963), who states that if the reaction between methyl chloride and copper-silicon is conducted under conditions such that some pyrolysis of the free hydrocarbon radicals occurs, halogenated products of the type SiRHX_2 appear in the product. Products in which the chlorine of silicochloroform is completely substituted are, however, known. For example, trimethoxysilane has been prepared from silicochloroform and methyl alcohol (Helfferich and Hausen, *Ber.*, 1924, **57**, 795). The corresponding trialkyl compounds have been obtained by the action of zinc alkyls on ethyl orthosilicate (Ladenburg, *Annalen*, 1872, **164**, 301; Pape, *Ber.*, 1881, **14**, 1873), and triphenylsilane has been prepared by various methods (Kipping and Murray, *J.*, 1929, 360; Reynolds, Bigelow, and Kraus, *J. Amer. Chem. Soc.*, 1929, **51**, 3067; Kraus and Eatough, *ibid.*, 1933, **55**, 5008). The preparations now described are of *ethyl*-, *phenyl*-, and *benzyl-dichlorosilane*, and *di-ethyl*-, *-phenyl*-, and *-benzyl-chlorosilane*, all of which were obtained by using the Grignard reaction. The alkyl-alkoxy-compounds described are related to the derivatives of silicochloroform by the fact that the alkyl (or aryl) groups are in both cases the only ones resistant to hydrolysis.

EXPERIMENTAL.

Silicochloroform was prepared by passing hydrogen chloride over powdered silicon at 380° (Booth and Stillwell, *J. Amer. Chem. Soc.*, 1934, **56**, 1529). The product was fractionated through a 16-inch Fenske column, the fraction of b. p. 31–34° being used in the following preparations.

Ethyl-dichlorosilane.—1.25 G.-mol. of ethylmagnesium bromide in 500 ml. of ether were added slowly to an ice-cooled, mechanically stirred solution of 135.5 g. of silicochloroform in 100 ml. of ether. The reaction mixture was heated under reflux for 4 hours, filtered, and the ethereal solution fractionated through a 16-inch Fenske column fitted with a reflux head, using a reflux ratio of 5 : 1. After removal of the ether, the following four fractions were obtained: (a) b. p. < 74° (8 g.), (b) b. p. 74.5–75.5° (39 g.), (c) b. p. 75.6–95° (6 g.), (d) b. p. 95–98° (5.5 g.). Analysis of fraction (b) gave: Si, 21.6; Cl, 54.7; C, 19.0; H, 4.7. ($\text{C}_2\text{H}_5\text{Cl}_2\text{Si}$ requires Si, 21.7; Cl, 54.9; C, 18.6; H, 4.7%). A determination of the molecular weight by the Dumas method gave 134.1 (Calc.: 129.1). The vapour-pressure curve of this compound between –17° and 70° was measured by means of an isoteniscope. The vapour-pressure data are represented by the equation $\log p = 7.6271 - 1648.2/T$; the b. p. was 74.2°, and Trouton's constant 20.4. Fraction (d) was shown by chlorine analysis to be a mixture of the mono- and the di-ethyl compound.

The silicochloroform derivatives described below were prepared by the same method, a suitable proportion of the appropriate Grignard reagent being used. In each case a series of fractions was obtained, one of which preponderated and corresponded to the desired product.

Diethylchlorosilane.—A fraction of b. p. 97–105° was refractionated through a Fenske column and gave this compound, b. p. 99–100°. The yield of purified product was 19% (Found: Si, 22.9; Cl, 28.9; C, 39.1; H, 9.1; *M*, by Dumas method, 126.8, 128.1. SiEt_2ClH requires Si, 22.9; Cl, 28.9; C, 39.15; H, 9.0%; *M*, 122.7). The equation to the vapour pressure curve for the range 0–94° was $\log p = 7.4195 - 1689.5/T$. The b. p. and Trouton's constant were 99.2° and 19.5, respectively.

Methyldichlorosilane.—The Grignard compound used was methylmagnesium chloride in *n*-butyl ether (Schmalfuss, *J. pr. Chem.*, 1924, **108**, 88). A fraction of b. p. 40.7° was obtained which proved to be the desired compound (Found: Si, 22.9; Cl, 61.9; C, 10.0; H, 4.6. SiMeCl_2H requires Si, 24.4; Cl, 61.7; C, 10.4; H, 3.5%). In this preparation three fractions were collected between 33° and 40.5°, and there was difficulty in obtaining a complete separation.

Phenyldichlorosilane.—A fraction of b. p. 118–119°/25 mm. was twice refractionated and gave a fraction, b. p. 65.0–65.3°/10 mm., of *phenyldichlorosilane* (Found: Cl, 40.2; C, 40.8; H, 3.5. SiPhCl_2H requires Cl, 40.0; C, 40.7; H, 3.4%).

Diphenylchlorosilane.—A fraction of b. p. 147–170°/10 mm. was refractionated and gave a fraction, b. p. 140–145°/7 mm., of the *chlorosilane* (Found: Si, 12.4; Cl, 16.3; C, 66.3; H, 5.3. SiPh_2ClH requires Si, 12.8; Cl, 16.2; C, 66.0; H, 5.1%).

Benzyl-dichlorosilane had b. p. 48°/2 mm. (Found: Si, 14.6; Cl, 37.0; C, 45.8; H, 4.2. $\text{Si}(\text{CH}_2\text{Ph})\text{Cl}_2\text{H}$ requires Si, 14.7; Cl, 37.0; C, 46.1; H, 4.2%), and *di-benzylchlorosilane* b. p. 146–148°/ca. 1 mm. (Found: Si, 11.5; Cl, 14.6; C, 67.5; H, 6.2; $\text{Si}(\text{CH}_2\text{Ph})_2\text{ClH}$ required Si, 11.4; Cl, 14.4; C, 68.1; H, 6.1%).

Alkylalkoxysilanes.—The four compounds of this type prepared were ethyltriethoxy-, diethyldiethoxy-, ethyltrimethoxy-, and diethyldimethoxy-silane. Ladenburg's method of preparation (*Annalen*, 1874, **173**, 143) using the reaction between diethyl zinc and the appropriate silicon ester is not convenient. Reaction between Grignard compounds and esters of orthosilicic acid has been used by Post and Hofrichter (*J. Org. Chem.*, 1939, **4**, 363), and Adrianov (*J. Gen. Chem. U.S.S.R.*, 1938, **8**, 558, 1255; 1939, **9**, 203) has prepared monosubstituted derivatives of the type $\text{SiR}(\text{OEt})_3$ by forming the Grignard compound *in situ* from the alkyl halide and magnesium in presence of ethyl orthosilicate, with which reaction then occurs. It is not possible by means of the ordinary Grignard reaction to substitute more than one of the alkoxy-groups of an orthosilicic ester.

The direct method of preparing compounds of this type is by reaction of the alkylsilicon chloride with an alcohol. The alcohol must be completely dry or much material of high molecular weight is obtained; e.g., Friedel and Crafts (*Annalen*, 1865, **136**, 203) found that in the reaction between silicon tetrachloride and methanol, two compounds, $\text{Si}(\text{OMe})_4$ and $\text{Si}(\text{MeO})_3\cdot\text{O}\cdot\text{Si}(\text{OMe})_3$, were obtained. Our preliminary experiments showed that on refluxing diethylsilicon dichloride and ethyl alcohol together, a considerable quantity of ethyl chloride was formed. This was isolated and characterised by its vapour-pressure curve; it is presumably formed in the secondary reaction between the alcohol and hydrogen chloride,

which yields the alkyl halide and water. Thus, even if the alcohol is initially dry, this water will inevitably lead to the production of more complex products. This difficulty has been overcome by using the sodium derivative of the alcohol in place of the alcohol itself.

The ethylsilicon halides required as intermediates were prepared by means of the Grignard reaction (Kipping, *J.*, 1907, **91**, 209). The sodium alkoxide was prepared by adding sodium in small pieces to an excess of the pure alcohol in a flask fitted with a reflux condenser, boiling off the excess of alcohol at the completion of the reaction, and removing the residual alcohol in an oil-pump vacuum. The product was a fine white powder.

The theoretical quantity of sodium ethoxide covered with ether was placed in a three-necked flask fitted with a mechanical stirrer, reflux condenser, and tap-funnel. The suspension was well stirred, and a solution of the theoretical quantity of ethylsilicon trichloride in an equal volume of ether was added slowly. The product was refluxed for an hour, transferred to a Kon flask and distilled. Ethyltriethoxysilane was collected at 155–160° and redistilled; b. p. 158–160°, yield 40% (Found : Si, 14.73, 14.65. Calc. for $C_6H_{18}O_3Si$: Si, 14.60%).

Similar preparations were carried out for diethyldiethoxysilane (b. p. 156–157°, yield, 40%), ethyltrimethoxysilane (b. p. 123°, yield 58%), and *diethyldimethoxysilane* (b. p. 130°, yield 70%) (Found : Si, 18.75, 18.96, 18.78; *M*, by Dumas method, 151.0, 153.3, 152.5. $C_6H_{16}O_2Si$ requires Si, 18.92%; *M*, 148.3).

The vapour-pressure curves of these compounds were studied by means of an isoteniscope technique, the results being tabulated below.

Compound.	Vapour-pressure relationship.	B. p.	Latent heat, cal./g.-mol.	Trouton's constant.
$SiEt(OEt)_3$	$\log p = 7.4759 - 1980.5/T$	158.9°	9085	21.03
$SiEt_2(OEt)_2$	$\log p = 7.3896 - 1940.5/T$	157.3	8883	20.64
$SiEt(OEt)_2$	$\log p = 7.8760 - 1968.1/T$	120.9	9007	22.86
$SiEt_2(OMe)_2$	$\log p = 7.912 - 2018.5/T$	128.1	9240	23.03

The authors wish to thank Imperial Chemical Industries Ltd. (Dyestuffs Division) for a grant in aid of this research.

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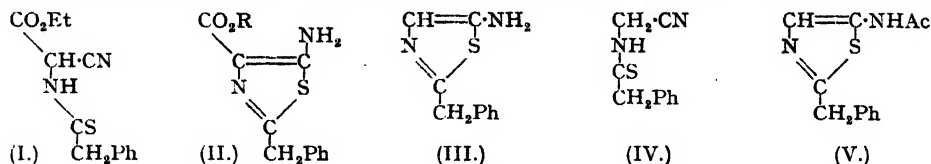
[Received, January 23rd, 1947.]

318. Studies in the Azole Series. Part I. A Novel Route to 5-Aminothiazoles.

By A. H. COOK, SIR IAN HEILBRON, and A. L. LEVY.

Dithiophenylacetic acid reacts with aminoacetonitrile or ethyl aminocynoacetate to give 5-amino- and 5-amino-4-carbethoxy-2-benzylthiazole, (III) and (II; R = Et), respectively. The behaviour of these bases towards acylating agents, nitrous acid, and in the case of the first-mentioned towards diazonium salts, nitrating agents, etc., is described. This seems a general synthesis of the hitherto almost unknown class of 5-aminothiazoles, 5-amino-4-phenyl- and 5-amino-4-carbethoxy-thiazole being obtained analogously.

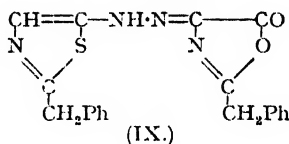
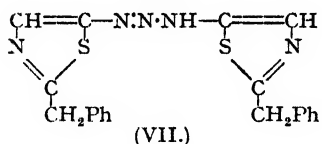
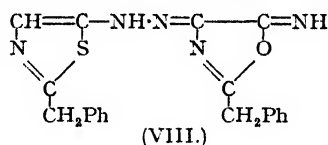
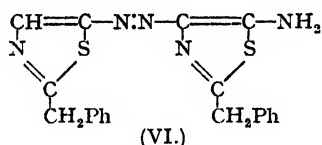
In connection with the study of penicillin (unpublished work) the reaction between sodium or methyl dithiophenylacetate and ethyl aminocynoacetate was examined. The product was at first thought to be ethyl phenylthionacetamidocynoacetate (I) but subsequent investigation showed that it was a base which could be better formulated as 5-amino-4-carbethoxy-2-benzylthiazole (II; R = Et). It formed a stable hydrochloride and on hydrolysis gave the corresponding acid (II; R = H). Hexoylation yielded 5-hexoamido-4-carbethoxy-2-benzylthiazole which still exhibited basic properties. Similarly, aminoacetonitrile and sodium dithiophenylacetate afforded an excellent yield of a base which by analogy is formulated as 5-amino-2-benzylthiazole (III). Its light absorption is compatible with this formulation and is



very similar to that of the corresponding 4-carbethoxy-compound above. It seems that phenylthionacetamidocetonitrile (IV) occurs as an intermediate and cyclises on warming, for a small amount of an alkali-soluble isomeride was isolated from the crude aminothiazole. The isomeride passed into the aminothiazole on being kept with hydrogen chloride in organic solvents and appears therefore to be the acyclic thioamide. This facile formation of 5-aminothiazoles is

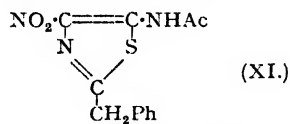
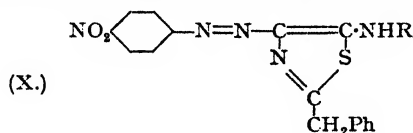
of interest as they have been so far almost unknown in the literature. Weidel and Niemilowicz (*Monatsh.*, 1895, 16, 721) described some degradation products of uric acid which are possibly derivatives of 5-aminothiazole. The only other noteworthy reference is to a series of derivatives of 5-amino-2-thiocarboxyamidothiazole ("chrysean") originating in the interaction of hydrocyanic acid and hydrogen sulphide (see Beilstein's "Handbuch", Vol. 27, 334; Arnold and Scaife, *J.*, 1944, 103). Jensen and Hansen (*Dansk Tids. Farm.*, 1943, 17, 189) and Ganapathi and Venkataraman (*Proc. Indian Acad. Sci.*, 1945, 22A, 343) have recently prepared some 5-aminothiazoles by orthodox reactions but the methods are not entirely satisfactory in scope and yield.

5-Amino-2-benzylthiazole formed a *hydrochloride* and on acetylation gave 5-acetamido-2-benzylthiazole (V) which had marked basic properties, and formed a *hydrochloride* and a *methiodide*; the latter clearly contained a "reactive" methylene group (in the adjacent benzyl substituent) and developed an intense cyanine-like colour on being heated with ethyl orthoformate under appropriate conditions. The 5-acetylsulphanilamido- and 5-sulphanilamido-compounds were also prepared. The sulphanilamide inhibited the growth of *Staph. aureus* at a limiting dilution of 1 : 50,000, but the inhibition was not complete, and even at 1 : 5000 abnormal agglutinated clumps of bacterial growth were observed. When (III) was treated with 1 mol. of nitrous acid there was some evolution of hydrogen sulphide and rapid appearance of a deep red-brown precipitate from which two products were isolated, $C_{20}H_{17}N_5S_2$ (A) and $C_{20}H_{17}ON_5S$ (B). The former formed brilliant crystals with a copper-like lustre and gave deep red solutions. The fact that (II) failed to behave similarly with nitrous acid supports structure (VI) rather than (VII) (cf. formation of aminoazobenzene). Formulation (VI), representing a diazonium salt coupling with a second molecule of amine in the 4-position, is perhaps novel to thiazole chemistry but strictly comparable with *ortho*-coupling of aromatic amines; it is supported by the fact that (V) couples with diazonium salts whereas (II) does not share this ability.



Product (B) formally contained a sulphur atom of (A) replaced by oxygen, but in view of its paler colour and altered light absorption it is tentatively formulated as the imino-compound (VIII). This formulation is in keeping with its behaviour on hydrolysis with cold dilute hydrochloric acid, which gave a compound $C_{20}H_{16}O_2N_5S$, obviously the oxazolone (IX).

It was mentioned above that (III) coupled with diazonium salts, and in illustration the orange-scarlet *azo*-compound (X; R = H) was prepared. The acetamido-compound (V) likewise coupled to give (X; R = Ac). Both *azo*-compounds were remarkable in giving intense violet colorations with caustic alkalis. When (V) was treated with nitrosyl chloride in acetic acid in an attempt to obtain the *N*-nitroso-derivative ("diazonium acetate") the sole product isolated was a nitro-compound which, in view of the ready reactivity of the 4-position, is obviously 4-nitro-5-acetamido-2-benzylthiazole (XI). In this connection it may be noted that nitrous acid not infrequently acts as a nitrating agent (*e.g.*, Hodgson, *J.*, 1932, 1812). Compound (XI) was also produced by direct nitration of (IV) with a nitric-sulphuric acid mixture, and by treatment of its *nitrate* with sulphuric acid in acetic acid solution.



Similar syntheses have been carried out by employing sodium dithioformate in place of dithiophenylacetate. As the reaction with aminoacetonitrile is complex, and in view of its special interest, it will form the subject of a separate communication. With ethyl aminocyno-

acetate reaction was facile, giving *5-amino-4-carbethoxythiazole* identical with the product obtained by heating the analogous 2-mercaptothiazole (see following paper) with Raney nickel. In the same way α -aminobenzyl cyanide and sodium dithioformate afforded *5-amino-4-phenylthiazole*, characterised as its *hydrochloride* and *acetyl* derivative, and likewise identified with the base obtained by desulphurising the analogous 2-mercaptothiazole.

It is noteworthy that all the ring-syntheses described here take place at room temperature, several of them in aqueous neutral solution.

Light-absorption data on the aminothiazole derivatives are recorded on p. 1598 in tabular form (cf. table in Part II).

Methyl ethylxanthate failed to exhibit the reactivity of the above dithio-acid derivatives towards α -amino-nitriles. On the other hand, it behaved as a "thioacylating" agent towards strong bases; e.g., it gives with morpholine *N-monothiocarboethoxymorpholine*.

EXPERIMENTAL.

(a) Crude ethyl aminocynoacetate (3 g.), prepared by reducing ethyl nitrosocynoacetate with amalgamated aluminium, was allowed to stand with methyl dithiophenylacetate (4 g.). Heat and thiol were evolved spontaneously and after a few minutes the mixture set to a mass of yellow needles. Treatment with a small quantity of ether gave almost pure *5-amino-4-carbethoxy-2-benzylthiazole* (II; R = Et) (3.6 g., a further 0.8 g. being recovered from the ethereal residues). It separated from ethanol in long colourless needles, m. p. 157° (Found: C, 59.8; H, 5.6; N, 10.9. $C_{13}H_{14}O_2N_2S$ requires C, 59.5; H, 5.4; N, 10.7%).

(b) Ethyl aminocynoacetate (5 g.) was shaken overnight in ether (50 c.c.) with sodium dithiophenylacetate (1 equiv.) in water (20 c.c.). Evaporation of the dried ethereal solution gave the free base, *5-amino-4-carbethoxy-2-benzylthiazole*, in poor yield, m. p. 156°. The thiazole (780 mg.) in dioxan (3 c.c.) and water (7 c.c.) was kept with 0.51N-sodium hydroxide (6 c.c.) overnight and then heated on the steam-bath for two hours. The filtrate was acidified with dilute hydrochloric acid, and the acid recrystallised from ethanol. *5-Amino-4-carboxy-2-benzylthiazole* separated in irregular prisms, m. p. 169° with violent evolution of gas (on slow heating) (Found: C, 56.5; H, 4.6; N, 12.0. $C_{11}H_{10}O_3N_2S$ requires C, 56.4; H, 4.3; N, 12.0%). Small quantities of this acid were obtained as a by-product during the preparation of the ester *via* sodium dithiophenylacetate.

The ester-thiazole (II) (0.52 g.) suspended in ethanol (5 c.c.) was treated with hydrogen chloride at -10° . After 12 hours at 20° the solution was evaporated in a vacuum, and the solid, m. p. 180°, washed with ether and crystallised from ethanol-ether. *5-Amino-4-carbethoxy-2-benzylthiazole hydrochloride* separated in rectangular plates, m. p. 180° (Found: C, 52.3; H, 5.5, 5.2; N, 9.7. $C_{13}H_{14}O_2N_2S \cdot ClH$ requires C, 52.5; H, 5.1; N, 9.4%). The ester-thiazole (II) (1 g.), *n*-hexoyl chloride (0.7 g.), and pyridine (20 c.c.) were heated together at $80-90^\circ$ for 2 hours, and the mixture evaporated in a vacuum. The residue was extracted with ether but the base remained oily on evaporation of solvent. Addition of ethereal hydrogen chloride gave a solid. *5-n-Hexamido-4-carbethoxy-2-benzylthiazole hydrochloride* crystallised from chloroform-light petroleum in clumps of feathery needles, m. p. 110°, which lost hydrogen chloride on heating to 56° in a vacuum and were dried at room temperature over phosphoric oxide (Found: C, 57.5; H, 6.7. $C_{16}H_{20}O_2N_2S \cdot ClH$ requires C, 57.5; H, 6.3%).

Aminoacetone nitrile sulphate (135 g.) in water (200 c.c.) was neutralised (brilliant-yellow) with potassium hydroxide (98 g.) in water (230 c.c.) in the cold. A neutral solution of potassium dithiophenylacetate (1 equiv.) in water (510 c.c.) was added with ether (1500 c.c.), the solution again brought to neutrality, and the whole shaken overnight. On separation of the ethereal layer and removal of solvent, the residual oil solidified (yield, 165 g., 98%). Crude *5-amino-2-benzylthiazole* (III) crystallised from ether-light petroleum or chloroform-light petroleum to form colourless needles, m. p. 87° (130 g.), which darkened on exposure to light (Found: C, 63.5; H, 5.5; N, 14.5. $C_{10}H_{10}N_2S$ requires C, 63.2; H, 5.3; N, 14.7%). The crude product, m. p. 83° (1.0 g.), was stood for 3 days in a mixture of dioxan (5.0 c.c.) and water (8.0 c.c.), and the product (0.2 g.) which separated recrystallised from ethanol to give colourless needles, m. p. 161° (decomp.), of *phenylthionacetamidoacetone nitrile* (IV) (Found: C, 63.0; H, 5.2; N, 14.8. $C_{10}H_{10}N_4S$ requires C, 63.2; H, 5.3; N, 14.7%). The compound was soluble in aqueous-alcoholic potash and was transformed by ethanolic hydrogen chloride into *5-amino-2-benzylthiazole hydrochloride*, m. p. and mixed m. p. 195° (decomp.).

The base could be conveniently converted into its hydrochloride by several methods; e.g., the base was covered with 3 vols. of warm ethanol and a little water and treated with a little ethanolic hydrogen chloride. This technique was only necessary when starting with the hydrochloride, which was insoluble in dry ethanol, but soluble in the wet solvent. The *hydrochloride* separated and could be recrystallised in the same manner, forming rectangular tablets, m. p. 194° (decomp.) (Found: C, 53.0; H, 4.9; N, 12.4. $C_{10}H_{11}N_2S \cdot ClH$ requires C, 53.0; H, 4.9; N, 12.4%).

5-Amino-2-benzylthiazole (1 g.) was treated with acetic anhydride (1 c.c.). The mixture became very hot, and on being rubbed with light petroleum set to a mass of yellowish crystals (yield, 1.2 g.). *5-Acetamido-2-benzylthiazole* (V) crystallised excellently from benzene, or a mixture of ethyl acetate, ethanol, or acetone with light petroleum, in square plates, m. p. 121° (Found: C, 61.8; H, 5.3; N, 11.7. $C_{12}H_{13}ON_2S$ requires C, 62.1; H, 5.2; N, 12.1%). It crystallised from water or aqueous solvents as a hydrate, m. p. $74-75^\circ$, in long hair-like needles.

The compound was set aside with cold ethanolic hydrogen chloride for 2 days. It passed into solution (4 hours) and *5-amino-2-benzylthiazole hydrochloride*, m. p. 194° (decomp.), crystallised cleanly from the colourless solution in good yield. The acetyl compound (0.95 g.) in concentrated hydrochloric acid (5 c.c.) was cooled to -10° and a little water added. The well-formed crystals were filtered off and

washed with a little acetone. 5-Acetamido-2-benzylthiazole hydrochloride separated from ethanol-acetone in laths, m. p. 204–206°, which were very stable and did not discolour at 250° (Found : C, 53.7; H, 5.0; N, 10.5. $C_{11}H_{13}ON_2S$ requires C, 53.6; H, 4.9; N, 10.4%). The same compound was obtained by adding ethereal hydrogen chloride to a solution of the base in acetone. The acetyl compound (1 g.) was refluxed with methyl iodide (2 c.c.) in acetone (10 c.c.) for 30 minutes, and the quaternary salt filtered off. It was insoluble in hot acetone and sparingly soluble in cold water, but crystallised from acetic acid (needles), water (rectangular tablets), or spirit (laths); 5-acetamido-2-benzylthiazole methiodide had m. p. 265° (Found : C, 41.9; H, 4.1; N, 7.4. $C_{11}H_{13}ON_2SI$ requires C, 41.7; H, 4.0; N, 7.5%). It gave intense blood-red colours with 1 : 3 : 3-trimethyl-2-methyleneindoline- ω -aldehyde or ethyl orthoformate in hot acetic anhydride-pyridine.

5-Amino-2-benzylthiazole (9.5 g.) in ice-cold ethanol (280 c.c.) was treated during 15 minutes with stirring with ice-cold *N*-sodium nitrite (50 c.c.) to which had been added 0.474*N*-hydrochloric acid (105 c.c., 1 equiv.). The solution became orange and deposited red-brown crystals; these increased as the solution was allowed to assume room temperature and were filtered off (yield, 11 g.) after 40 minutes; some evolution of hydrogen sulphide was noticed. The solid was extracted with boiling benzene (100 c.c.); the residue (3.5 g.) of bright orange-red powder (A) could be supplemented by a small quantity obtained from the alcoholic mother-liquor above. (A) was insoluble in water, ether, and light petroleum, slightly soluble in hot ethanol, acetone, chloroform, or ethyl acetate, readily soluble in hot acetic acid. It crystallised from acetic acid, nitrobenzene or much toluene in coppery, rectangular tablets or needles, m. p. 213° (Found : C, 61.2; H, 4.2; N, 17.4. $C_{20}H_{17}N_3S_2$ requires C, 61.4; H, 4.4; N, 17.9%), formulated as the *azo*-compound (VI). Light absorption (chloroform) : λ max. = 281, 291, 308 $m\mu$, $E_{1\%}^{1cm}$ = 230; 453 $m\mu$, $E_{1\%}^{1cm}$ = 660. It was insoluble in sodium hydrogen carbonate solution, apparently slowly changed by hot aqueous sodium hydroxide, gave a brown hydrochloride when its chloroform solution was treated with ethanolic hydrogen chloride, and gave a deep red solution in concentrated sulphuric acid. The benzene mother-liquors (above) were chromatographed on alumina; material (B), obtained from a sharp brown band on developing with benzene-ethanol (1 : 1), recrystallised from chloroform-light petroleum in pale yellow rectangular plates, m. p. 139° (Found : C, 64.2; H, 4.7; N, 18.4. $C_{20}H_{17}ON_2S$ requires C, 64.0; H, 4.6; N, 18.6%); in a later preparation the chromatography could be omitted. (B) is perhaps best formulated as the *imino*-derivative (VIII); it was insoluble in cold water, aqueous sodium hydrogen carbonate, and sodium hydroxide, but was changed by warm dilute mineral acid. Light absorption (ethanol) : λ max. = 265, 322 $m\mu$, $E_{1\%}^{1cm}$ = 200, 250. The imino-derivative was dissolved in warm methanol and diluted with warm 2*N*-hydrochloric acid. On cooling, the *oxazolone* derivative (IX) separated, filling the tube with crystals, m. p. 116°, which recrystallised from methanol in platelets, m. p. 114–116° (Found : C, 62.4; H, 4.6; N, 13.9. $C_{20}H_{15}O_2N_2S$, MeOH requires C, 61.8; H, 4.9; N, 13.7%). Heating at 100° in a vacuum raises the m. p. to 202–205°. Light absorption (ethanol) : λ max. = 301 $m\mu$, $E_{1\%}^{1cm}$ = 290.

5-Amino-2-benzylthiazole (1 g.) in ethanol (30 c.c.) containing potassium acetate was treated with a diazonium salt solution prepared with *p*-nitroaniline (0.7 g.) in excess of 8% hydrochloric acid. The vessel was immediately filled with a highly crystalline scarlet precipitate of the *azo*-dye (2.3 g., m. p. 140°). It crystallised fairly well from ethanol, isopropanol, *tert*-butanol, or chloroform-ether; it also crystallised from acetic acid but was partly transformed into green crystals, though the nature of this change is obscure. 5-Amino-4-*p*-nitrobenzenazo-2-benzylthiazole (X; R = H) crystallised best from toluene containing a little nitrobenzene and then formed rust-brown needles, m. p. 158° on rather rapid heating (Found : C, 56.8; H, 3.6; N, 20.3. $C_{16}H_{13}O_2N_3S$ requires C, 56.6; H, 3.9; N, 20.6%); it gave an intense purple solution with alkali.

Diazotised *p*-nitroaniline was coupled similarly with 5-acetamido-2-benzylthiazole. Coupling was slower and the colour (orange) less intense than with the aminothiazole. The dye was moderately soluble in ether or ethanol, easily soluble in the cold in chloroform, ethyl acetate or acetone. 5-Acetamido-4-*p*-nitrobenzenazo-2-benzylthiazole (X; R = Ac) crystallised from aqueous acetone or benzene in laths, m. p. 175–176° (Found : C, 57.2; H, 4.1; N, 18.0. $C_{18}H_{15}O_2N_3S$ requires C, 56.7; H, 4.0; N, 18.4%); it also gave a magnificent purple colour with sodium hydroxide.

5-Amino-2-benzylthiazole (1.9 g.) and acetylsulphanilyl chloride (2 g.) were kept together in pyridine (5 c.c.) overnight, and the solution poured into water. The oil soon crystallised (yield, 3.2 g.); 5-acetylsulphanilamido-2-benzylthiazole crystallised from ethyl acetate containing a little ethanol, or from aqueous acetone, in needles, m. p. 189° (Found : C, 55.7; H, 4.4. $C_{18}H_{17}O_2N_3S_2$ requires C, 55.8; H, 4.4%). The acetylsulphanilamide (1.5 g.) was refluxed with 2*N*-hydrochloric acid (20 c.c.) for 0.5 hour. Filtration from a little gum and addition of concentrated aqueous sodium acetate gave 5-sulphanilamido-2-benzylthiazole (1 g.), which crystallised from dilute ethanol in prismatic needles, m. p. 182° (Found : C, 55.4; H, 4.4; N, 11.8. $C_{10}H_{15}O_2N_3S_2$ requires C, 55.6; H, 4.3; N, 12.2%).


5-Acetamido-2-benzylthiazole (1.25 g.) in 0.5*N*-hydrochloric acid (10 c.c.) and dioxan to give a permanent solution was treated with *N*-sodium nitrite (10 c.c.) at 0°. After standing for one week the brownish needles were collected and recrystallised from aqueous methanol. This compound was 5-acetamido-2-benzylthiazole nitrate and was obtained from the base and nitric acid in alcohol; it separated in colourless needles, m. p. 111° (decomp.) (Found : C, 48.9; H, 4.3; N, 14.2. $C_{12}H_{13}O_4N_3S$ requires C, 48.8; H, 4.4; N, 14.2%). When it was dissolved in acetic acid containing concentrated sulphuric acid and the solution poured into water it was converted into 4-nitro-5-acetamido-2-benzylthiazole (X1), which crystallised from ethanol in needles, m. p. 152° (Found : C, 52.5; H, 4.0; $C_{12}H_{11}O_3N_3S$ requires C, 52.0; H, 4.0%). 5-Acetamido-2-benzylthiazole (4 g.) in acetic anhydride (10 c.c.) and acetic acid (30 c.c.) containing fused sodium acetate (4 g.) and phosphoric oxide (0.5 g.) was cooled to 8°, and nitrosyl chloride in acetic acid added (0.5 hr.) until the red colour persisted. The mixture was allowed to stand at room temperature for 1 hour and was then poured into water (cf. France, Heilbron, and Hey, *J.*, 1940, 369). On standing, crystals separated, m. p. 135–140° raised to 152° on crystallisation from benzene and light petroleum (charcoal). 5-Acetamido-2-benzylthiazole (1.0 g.) was dissolved in acetic acid (10 c.c.) containing concentrated sulphuric acid (1 c.c.), and concentrated nitric acid (0.5 c.c.) added. After

30 hours at room temperature the mixture was poured into iced water, and the 4-nitrothiazole, m. p. 152°, collected. It was soluble in aqueous sodium hydroxide to give a red solution.

α -Aminobenzyl cyanide (1.3 g.) in ether (10 c.c.) was shaken with sodium dithioformate (1.0 g.) in water (10 c.c.) for 2 days. 5-Amino-4-phenylthiazole (0.7 g.) separated in colourless needles, m. p. 135–136°, and was recrystallised from benzene; a further quantity of crude material (0.4 g.) was recovered from the ether [Found : C, 61.6; H, 4.6; M (Rast), 170. $C_9H_8N_2S$ requires C, 61.4; H, 4.6%; M, 176]. The substance coupled with diazotised aniline in methanol solution containing sodium acetate. Treatment of a warm benzene solution of the base with acetic anhydride and addition of light petroleum (b. p. 40–60°) gave 5-acetamido-4-phenylthiazole, m. p. 147–148°, crystallising from benzene in sheaves of colourless needles (Found : C, 60.4; H, 4.7. $C_{11}H_{10}ON_2S$ requires C, 60.5; H, 4.6%). Solution of 5-amino-4-phenylthiazole in acetic acid and addition of a little ethanolic hydrogen chloride caused rapid separation of 5-amino-4-phenylthiazole hydrochloride (Found : C, 51.1; H, 4.1. $C_9H_8N_2S \cdot HCl$ requires C, 50.8; H, 4.2%). The compound crystallised from acetic acid in needles, m. p. 218° (decomp.), and gave a blue precipitate with sodium nitrite in aqueous solution.

Crude ethyl aminocynoacetate (ca. 5 g.) in ether (100 c.c.) was shaken with sodium dithioformate (4 g.) in water (50 c.c.), and the product kept overnight at 0°. The crystals recrystallised from ethanol to give 5-amino-4-carbethoxythiazole as prisms, m. p. 163.5° (Found : N, 16.3; S, 18.6. $C_6H_6O_2N_2S$ requires N, 16.3; S, 18.6%); the m. p. was undepressed by the product of desulphurisation of 5-amino-2-mercapto-4-carbethoxythiazole (Part II). The amine (0.5 g.) was boiled with acetic anhydride (0.5 c.c.) for 30 mins., and the solution poured on ice. 5-Acetamido-4-carbethoxythiazole crystallised from water in long needles, m. p. 123° (Found : C, 44.7; H, 4.4; S, 15.0. $C_8H_{10}O_3N_2S$ requires C, 44.9; H, 4.7; S, 15.0%).

Methyl ethylxanthate (1.4 g.) and morpholine (0.9 g.) were mixed. Heat and methylthiol were evolved and crystals separated. N-Monothiocarboethoxymorpholine was precipitated completely by adding ethanol and water, and recrystallised from aqueous ethanol or light petroleum in long needles, m. p. 58–59° (Found : C, 48.2; H, 7.4; N, 8.4. $C_7H_{13}O_2NS$ requires C, 48.0; H, 7.4; N, 8.0%).

Light Absorption of Thiazoles, 

Substituent :			Solvent.	$\lambda_{max.}$	$E_{1\%}^{1cm.}$
2.	4.	5.			
CH_2Ph	H	NH_2	EtOH	281	325
CH_2Ph	CO_2Et	NH_2	"	290	300
				280	460
				290	390
H	CO_2Et	NH_2	"	280	650
H	Ph	NH_2		280	660
				290	630
CH_2Ph	H	NHAc	"	272 (inflexion)	485
				278	535
CH_2Ph	NO_2	NHAc	$CHCl_3$	245	690
				350	370

We thank I.C.I. Ltd. (Dyestuffs Division) for gifts of chemicals, and Dr. E. A. Braude for the absorption spectra.

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[Received, January 23rd, 1947.]

319. Studies in the Azole Series. Part II. The Interaction of α -Amino-nitriles and Carbon Disulphide.

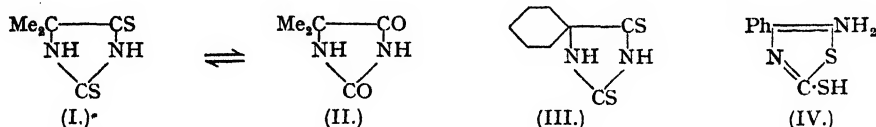
By A. H. COOK, SIR IAN HEILBRON, and A. L. LEVY.

The reaction between α -amino-nitriles and carbon disulphide leads, according to conditions, to 5-amino-2-mercaptothiazoles or derivatives thereof, or to dithiohydantoins. The former may be transformed into dithiohydantoins, or hydrolysed to α -amino-acids. The constitutions of representative compounds were confirmed by desulphurisation to 5-aminothiazoles or iminazoles. The further chemistry of 5-amino-2-mercapto-4-phenylthiazole (IV), in particular including its acetylation, methylation, condensation with aldehydes or ketones, and oxidation, is described, and some implications of these reactions are discussed.

THE preceding paper described the preparation and properties of 5-amino-2-benzylthiazole and some near derivatives. The preparative method, *viz.*, interaction of aminoacetonitrile and sodium or methyl dithiophenylacetate, promised to be of extensive application and the present communication deals with a detailed study of the reaction between α -amino-nitriles and carbon disulphide, which may be regarded as the anhydride of dithiocarbonic acid.

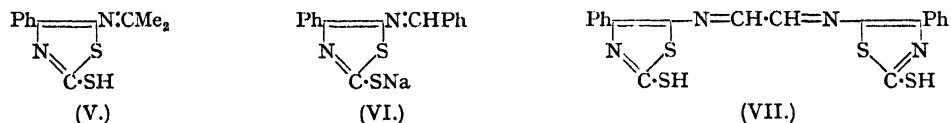
This reaction is stated (U.S.P. 2,143,816) to yield dithiohydantoins but the only example

described in detail is that with α -aminoisobutyronitrile. That the product was (I) was proved by oxidising it to the known 5:5-dimethylhydantoin which was reconverted into the thio-compound by heating with phosphorus pentasulphide (Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090; cf. also Jacobson, *ibid.*, 1945, **67**, 1996). According to B.P. 512,629, *spirodithiohydantoin*s, e.g., (III), are similarly formed from amino-nitriles derived from cyclic ketones. It is interesting in view of these findings to recall that Bücherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5) had, by analogy with the formation of hydantoins from carbon dioxide and moist α -amino-nitriles, unsuccessfully attempted the similar formation of dithiohydantoins.



Because of complications in the reaction between aminoacetonitrile and carbon disulphide, attention was first directed to the reaction between carbon disulphide and α -aminobenzyl cyanide; this base is easily accessible from benzaldehyde, hydrogen cyanide, and ammonia (Dubsy, *Ber.*, 1919, **52**, 232). The reaction was easily effected at room temperature, carbon disulphide being used in aqueous suspension. The product was a high-melting yellow crystalline solid, $\text{C}_9\text{H}_8\text{N}_2\text{S}_2$, which was obviously not 5-phenyl-2:4-dithiohydantoin. Contrary to this formulation it readily condensed with acetone to give a new compound, $\text{C}_{12}\text{H}_{12}\text{N}_2\text{S}_2$, which quickly reverted to the first material in presence of dilute mineral acid. This, together with other facts noted below, indicated that the primary product is more properly formulated as 5-amino-2-mercapto-4-phenylthiazole (IV), and the condensation product as the *Schiff's base* (V). It is interesting to note that the analogous benzaldehyde *Schiff's base* is formed in small yield by the direct interaction at room temperature of benzaldehyde, ammonium cyanide, and carbon disulphide in ethanol. The thiazole (IV) itself condensed equally easily with other aldehydes and ketones such as acetophenone and cinnamaldehyde to give yellow-orange, highly crystalline condensation products. All these bases were sensitive to mineral acid but more stable towards alkali, giving sparingly soluble sodium salts. Thus the benzaldehyde salt (VI) was obtained in yellow crystals, almost insoluble in water but soluble in ethanol, ethyl acetate, or acetone like metallic derivatives of dithiocarbamic acids to which they are obviously allied (cf. Delépine, *Bull. Soc. chim.*, 1908, **3**, 643).

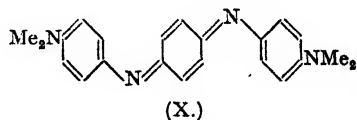
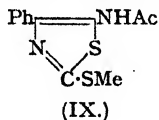
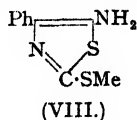
The chromophoric properties of the 5-aminothiazole system were particularly well illustrated by reaction of (IV) with glyoxal whereby the deep-red *bisazomethine* (VII) was readily formed; it gave a deep purple disodium salt soluble in acetone with an intense blue colour. Exactly similar red colours were observed on boiling (IV) in pyridine with diacetyl, phenylmethylglyoxal, or benzil, the colours in each case deepening considerably in presence of alkali. Condensation proceeded remarkably easily between the hydrochloride of (IV) and carbonyl compounds in cold methanol; in this way *Schiff's bases* derived from phenanthraquinone and isatin were also obtained.



Hydrolysis of (IV) under moderately vigorous acid conditions gave α -aminophenylacetic acid and carbon disulphide. It was weakly basic and pseudoacidic; it formed a *hydrochloride*, and when treated with methyl sulphate in an aqueous alkaline medium was converted into 5-amino-2-methylthio-4-phenylthiazole (VIII). Similar alkylation with benzyl chloride afforded 5-amino-2-benzylthio-4-phenylthiazole. Methylation was effected more easily by refluxing with methyl iodide in ethanol, the *hydriodide* of (VIII) being obtained. When the first method was used, a water-soluble methosulphate formed a by-product. This compound could still be diazotised and coupled with β -naphthol and is formulated as 5-amino-2-methylthio-4-phenylthiazole methosulphate. It condensed remarkably easily with compounds containing reactive methyl or methylene; for instance, on mixing with an aqueous solution of quinaldine methiodide, methylthiol was evolved and a cyanine dyestuff separated in purple crystals. This and similar reactions will be reported in detail in due course.

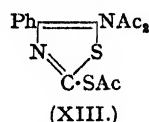
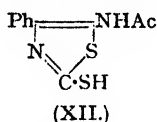
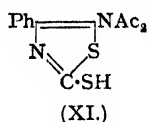
Diazotisation of (VIII) gave a diazonium salt solution which coupled readily with

5-amino-2-benzylthiazole to a deep red dye. Similarly, by using β -naphthol, the crystalline *azo-dye* was isolated. Condensation of (VIII) with glyoxal in ethanol gave the *SS'-dimethyl* derivative of (VII) which separated almost immediately as maroon crystals. A better reagent was a cold methanolic solution of the hydrochloride of (VIII), which reacted immediately with numerous carbonyl compounds (see experimental portion), to give the corresponding *Schiff's bases*. It may be mentioned that a colour with glyoxal under these conditions seems diagnostic of the presence of a 5-amino-2-mercaptothiazole. Acetylation of (VIII) gave 5-acetamido-2-methylthio-4-phenylthiazole (IX), also obtained by the action of alcoholic methyl iodide on 5-acetamido-2-mercapto-4-phenylthiazole (see below); (IX) was relatively stable to boiling sodium hydroxide and ethanolic hydrogen chloride.



Many attempts were made to condense 5-amino-2-mercapto-4-phenylthiazole (IV) with *p*-nitrosodimethylaniline, a variety of products being obtained under different conditions. Insofar as they were examined, however, the reaction seemed one of oxidation-reduction rather than condensation. For instance, in pyridine considerable heat was evolved and a deep red colour developed; analysis of the red-brown crystalline product agreed best, though not completely satisfactorily, with the *quinoneimine* (X). This formed a labile hydrochloride which on more prolonged treatment with ethanolic hydrochloric acid was converted into the bis-hydrochloride of *p*-aminodimethylaniline.

When (IV) was acetylated for a short time under mild conditions, an alkali-soluble monoacetyl derivative formulated as 5-acetamido-2-mercapto-4-phenylthiazole (XII) was obtained, though perhaps as a result of hydrolysis of the diacetyl derivative. More drastic treatment gave an alkali-labile diacetyl derivative regarded as 5-diacetylamino-2-mercapto-4-phenylthiazole (XI), and still more prolonged treatment gave a triacetyl derivative. Both di- and tri-acetyl derivatives reverted to (XII) on mild hydrolysis and the triacetyl compound must, it appears, be formulated as 5-diacetylamino-2-acetylthio-4-phenylthiazole (XIII).



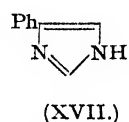
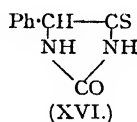
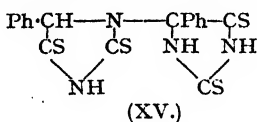
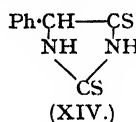
When (IV) was allowed to stand with alkaline hydrogen peroxide it was converted into a red sodium salt, from which the free compound was obtained as an orange pigment. Treatment of the sodium salt with methyl sulphate gave a non-acidic orange *dimethyl* derivative. Analyses suggested empirical formulae of the type $C_{38}H_{22}ON_6S_4$ and $C_{38}H_{26}ON_6S_4$ respectively for these products (*i.e.*, four thiazole nuclei with two methyl groups or methylatable hydrogen atoms) although the molecular weight of the methyl derivative in camphor seemed to be 306; there is as yet insufficient evidence to suggest detailed structures for these compounds. The same acidic product was formed on aerial oxidation of (IV) or with sodium nitroprusside in alkaline solution, and in surprisingly good yield by treating (IV) with alkali and acetylsulphanil chloride.

Many other colour reactions of the mercaptothiazole were observed; *e.g.*, intense red colours were developed on warming with benzoyl chloride or 2 : 4-dinitrochlorobenzene but the nature of the products was not investigated.

In view of the antibacterial activity of certain cyclic thiols (Gibbs and Robinson, *J.*, 1945, 925), the effect of (IV) was examined. At a concentration of 1 mg./c.c. in neutral phosphate buffer it showed considerable inhibition of the growth of *Staph. aureus*.

Convincing evidence of the correctness of the thiazole structures was afforded by treating (IV) and its derivatives with alkali and Raney nickel respectively. For example, when (IV) was brought into contact with the latter reagent in hot ethanol, removal of one atom of sulphur proceeded spontaneously to give the known 5-amino-4-phenylthiazole (Part I, preceding paper), which, unlike the parent mercapto-compound, gave no characteristic colours with glyoxal. The base was also obtained by desulphurising the corresponding acetone or benzaldehyde *Schiff's bases* of (IV), and the acetyl derivative was smoothly prepared by desulphurising 5-acetamido-2-mercapto-4-phenylthiazole.

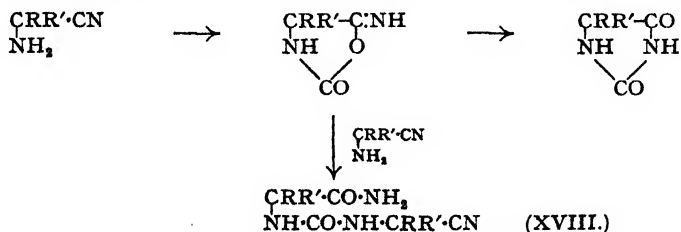
When (IV) was boiled with aqueous ammonia the solution soon ceased to give the characteristic Schiff's base with glyoxal, and an isomeride of the original base was isolated; from results described below this is formulated as 2:4-dithio-5-phenylhydantoin (XIV). The same dithiohydantoin was obtained by treatment of (IV) with caustic alkali, together with 1':5-bis-(2:4-dithio-5-phenylhydantoin) (XV). The latter structure is assigned by analogy with diphenylhydantoin, formed by the action of alkali on 5-phenylhydantoin (Pinner, *Ber.*, 1888, 21, 2320; Gabriel, *Annalen*, 1906, 250, 118). (XV) was more readily obtained by the action of mild oxidising agents on the dithiohydantoin. Treatment of 5-amino-2-methylthio-4-phenylthiazole (VIII) with alkali led to elimination of methylthiol and formation of 4-thio-5-phenylhydantoin (XVI) with the same properties as that described by Johnson and Chernoff (*J. Amer. Chem. Soc.*, 1912, 34, 1212). The structure of (XIV) was indicated by its pseudoeidic and non-basic character and especially by its behaviour with Raney nickel. By contrast with the parent thiazole (IV) both sulphur atoms were labile, the product being 5(4)-phenyliminazole (XVII), also obtained from (XV) by similar means. Further examples of this facile synthesis of iminazoles of more general interest will be described in later communications. An attempt was made to synthesise (XIV) by the action of phosphorus pentasulphide on 5-phenylhydantoin, but surprisingly the product proved to be 5(4)-phenyliminazole (XVII). Both (XIV) and (XV) were remarkably stable to acid and alkaline hydrolysis, more so than their oxygen analogues.



When α -aminopropionitrile was treated with carbon disulphide under conditions comparable with those in the foregoing experiments, two products were obtained in approximately equal yield. One was a pseudo-acid with no observable basic properties and is probably to be formulated as 2:4-dithio-5-methylhydantoin. The second product evolved acetaldehyde on warming with mineral acid and is regarded as the *acetaldehyde Schiff's base* of 5-amino-2-mercapto-4-methylthiazole, treatment with hydrogen chloride giving 5-amino-2-mercapto-4-methylthiazole *hydrochloride* characterised by the scarlet colour with glyoxal. The formation of the acetaldehyde Schiff's base is clearly similar to that of the corresponding phenyl compound described above. Indeed, when the present reaction was deliberately carried out in presence of acetaldehyde, dithiohydantoin formation was completely inhibited and the aminothiazole derivative was the sole product.

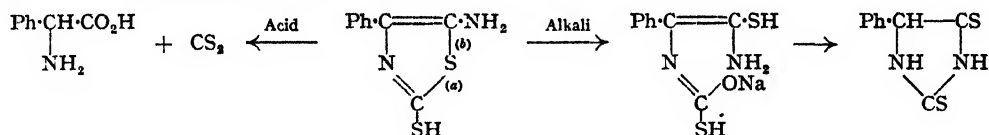
On similar reaction of ethyl aminocynoacetate (cf. preceding paper) a product was easily isolated which although failing to diazotise under normal conditions did so in concentrated sulphuric acid solution and must be formulated as 5-amino-2-mercapto-4-carbethoxythiazole. This was confirmed by treatment with Raney nickel, whereby it was converted into 5-amino-4-carbethoxythiazole, identified with the material described in the preceding paper. When the condensation with carbon disulphide was carried out in acetone solution an unstable intermediate, probably the acetone Schiff's base, was obtained which passed into the above aminomercaptocarbethoxythiazole on recrystallisation.

The above examples indicate therefore a general reaction leading to aminothiazoles or dithiohydantoins according to conditions. It is possible, moreover, that analogous reactions take place between α -amino-nitriles and carbon dioxide, for a facile combination of carbon dioxide and α -aminobenzyl cyanide was observed, giving a surprisingly stable *product* having a composition corresponding to $(\text{C}_6\text{H}_5\text{N}_2)_2\text{CO}_2$. Bucherer and Steiner (*J. pr. Chem.*, 1934, 140, 291) observed that the interaction of carbon dioxide and α -aminoisobutyronitrile led to 5:5-dimethylhydantoin together with a second product tentatively regarded as (XVIII); R, R' = Me).



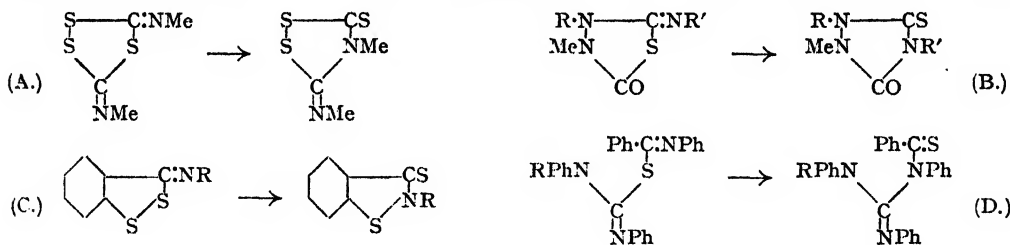
The genesis of both products is readily understood if the formation of an imino-oxazolidone as an intermediate comparable with the above aminothiazoles be assumed. In this case the product from α -aminobenzyl cyanide is best regarded as (XVIII; R = H, R' = Ph). The rearrangement of the imino-oxazolidone to the hydantoin may be compared with the transformation of *o*-cyanobenzoic acid into phthalimide presumably *via* an imino-compound (Sandmeyer, *Ber.*, 1885, 18, 1499).

It will be noticed that in the above examples an aminothiazole was obtained in the case of the reactions with α -aminobenzyl cyanide or ethyl aminocynoacetate and that in the former instance a medium such as alkali or moist pyridine was required to complete the transformation into the dithiohydantoin. This reflects a stabilising influence of the phenyl and the carbethoxyl group on the thiazole ring and, secondly, suggests that the mechanism of the transformation consists first in fission of the bond (a) :



The closely analogous cyclisation of α -carbethoxyaminophenylthioacetamide in alkali to 4-thio-5-phenylhydantoin (XVI) has been described by Johnson and Chernoff (*loc. cit.*). When 5-amino-2-mercapto-4-phenylthiazole was boiled, on the other hand, with dilute mineral acid, α -aminophenylacetic acid and carbon disulphide were formed indicating fission at (b) which may be preceded by elimination of ammonia. This indirect hydrolysis of an α -amino-nitrile has been applied to the preparation of more complicated α -amino-acids which will be described elsewhere. The process offers advantages in that the aminothiazole derivatives are more readily isolated and crystallise easily compared with α -amino-nitriles.

The above transformation into a dithiohydantoin presents no essential novelty, being paralleled in other heterocyclic series of varying complexity. Thus the transformation (A) was noted by Freund (*Annalen*, 1895, 285, 154), (B) by Busch and Limpach (*Ber.*, 1911, 44, 560),



and (C) by McClelland and Salkeld (*J.*, 1936, 1143). The observation of "acyclic" transformations of this kind, of which (D) is a recent example (Rivie and Langer, *Helv. Chim. Acta*, 1943, 26, 1722), points to a probable oversimplification in the mechanism suggested under (a) above.

The absorption spectra of most of the above thiazoles are tabulated below. A practically invariable feature is a band at *ca.* 2900 Å. which reflects a strong bathochromic effect of the 5-amino-grouping, as thiazoles and alkylthiazoles exhibit a band at *ca.* 2400 Å. (Ruehle, *J. Amer. Chem. Soc.*, 1935, 57, 1887; Jones, Robinson, and Strachan, *J.*, 1946, 91).

EXPERIMENTAL.

Reactions with α -Aminobenzyl Cyanide.—Redistilled benzaldehyde (367 g.) was mixed with anhydrous hydrogen cyanide (103 g.), and aqueous ammonia (*d* 0.880, 1—2 c.c.) added to initiate the reaction, which was moderated by strong cooling. After the mixture had stood at room temperature for 7 hours, liquid ammonia (65 g.) dissolved in ethanol (150 c.c.) was added and the mixture stood for 1 day at room temperature and 2 days at 0°. The large plates of α -aminobenzyl cyanide (115 g.) which had separated were filtered off and washed with plain spirit (500 c.c.); m. p. 55°. The syrupy filtrate was treated with carbon disulphide (200 c.c.), and large yellow crystals (126 g.) of the thiazole (see below) were soon deposited. This crude product (m. p. 259°, decomp.) contained about 8% of the corresponding benzylidene derivative, which can be removed as its insoluble sodium salt by treatment with aqueous sodium hydroxide.

α -Aminobenzyl cyanide (13.5 g.) was refluxed in ether (250 c.c.) with carbon disulphide (10 g.) for 8 hours. The yield of yellow crystals (12.8 g.) was augmented by standing the filtrate with carbon

disulphide (10 g.) overnight (total yield, 19.6 g., 93%). In another preparation the nitrile (20 g.) in ether (500 c.c.) was kept with carbon disulphide (11 c.c.) for 2½ days, and the crystals (26 g.) collected; on longer standing a further 4 g. separated (total yield, 95%).

α -Aminobenzyl cyanide hydrochloride (1.0 g.) in water (10 c.c.) was neutralised to phenolphthalein with 2*N*-sodium hydroxide, and carbon disulphide (0.5 c.c.) and a little methanol added. After 17 hrs.' shaking at room temperature, crude 5-amino-2-mercapto-4-phenylthiazole (IV) (0.65 g.) was obtained. This was sparingly soluble in ethanol, from which it separated in bright yellow tablets, and in most common solvents, but crystallised well from pyridine-ethanol in needles, and then had m. p. 261–262° (decomp.) (Found : C, 52.3; H, 3.9. $C_9H_8N_2S_2$ requires C, 51.9; H, 3.9%). It was converted into a very insoluble product in boiling nitrobenzene but dissolved in alkali and was precipitated unchanged by acid; it was soluble in aqueous baryta, a barium salt soon crystallising in plates. The thiazole dissolved in concentrated sulphuric acid to a lemon-yellow solution and deposited a chocolate-brown precipitate on dilution. Treatment with benzoyl chloride or 2 : 4-dinitrochlorobenzene in dioxan gave an intense red colour.

The thiazole (IV) was shaken with ethanolic hydrogen chloride. After about 1 hour the flask was filled with a thick cream of hydrochloride. 5-Amino-2-mercapto-4-phenylthiazole hydrochloride could be recrystallised from ethanol-etheral hydrogen chloride but crystallised best from methanol on adding concentrated hydrochloric acid; it formed colourless needles, m. p. 189° (decomp.) (Found : C, 44.0; H, 4.0; N, 11.1. $C_9H_8N_2S_2Cl$ requires C, 44.2; H, 3.7; N, 11.4%).

The thiazole (IV) was refluxed with excess of acetone. After 1 hour a clear solution was obtained which was evaporated in a vacuum and the residue taken up in ethanol. On cooling, the Schiff's base (V) separated in pale yellow needles, m. p. 187°, in almost theoretical yield (Found : C, 58.2; H, 5.1; N, 10.9. $C_{12}H_{12}N_2S_2$ requires C, 58.1; H, 4.8; N, 11.3%). The same product (1 g.) was obtained when α -aminobenzyl cyanide (1 g.) was refluxed with carbon disulphide (5 c.c.) and acetone (20 c.c.) for 3 hours, and the solution evaporated until it crystallised. 5-Amino-2-mercaptothiazole was refluxed overnight in ethanol with an excess of acetophenone. On filtering and cooling an excellent yield of the acetophenone Schiff's base crystallised. It could be recrystallised from ethanol containing dioxan in yellow needles, m. p. 212° (Found : C, 65.5; H, 4.2; N, 8.6. $C_{17}H_{14}N_2S_2$ requires C, 65.8; H, 4.5; N, 9.0%); it was also formed, though in poorer yield, on boiling the components in pyridine. The aminothiazole (IV) (2 g.) was refluxed with ethanol (50 c.c.) and cinnamaldehyde (2 g.) for 5 mins., the contents of the flask then having set almost solid with a mass of orange crystals (2.7 g.). The cinnamaldehyde Schiff's base was insoluble in ethanol, moderately soluble in hot toluene, chloroform, acetone, or ethyl acetate, from which it crystallised in needles, or in acetic acid from which it separated in spear-shaped crystals. It was best crystallised from ethanol-dioxan (2 : 1) in orange needles; m. p. 226° (Found : C, 68.6, 66.6; H, 4.5, 4.9; N, 8.9. $C_{18}H_{14}N_2S_2$ requires C, 67.1; H, 4.4; N, 8.7%). It gave a red crystalline sodio-derivative crystallising from aqueous ethanol, and an intense red colour with ethanolic hydrogen chloride or concentrated sulphuric acid, but dilute acid quickly hydrolysed it to its components.

The benzaldehyde Schiff's base, which could be prepared in the usual manner, crystallised from ethanol containing a little water in fine yellow needles, m. p. 226–229° (slow heating) after contracting at 205° (Found : C, 65.0; H, 4.1; N, 9.55. $C_{16}H_{12}N_2S_2$ requires C, 64.9; H, 4.1; N, 9.5%). Benzaldehyde (10.5 g.) in ethanol (50 c.c.) was kept over-night with ammonium cyanide (4.5 g.) and carbon disulphide (8 g.). The Schiff's base (4.0 g.) separated and a further 2.5 g. separated after 1 week. The benzaldehyde Schiff's base dissolved in 2*N*-sodium hydroxide to a lemon-yellow solution which on standing deposited a yellow solid. This sodium salt (VI) was soluble in acetone, ethanol, or ethyl acetate and was purified by extraction with acetone and precipitation with light petroleum or by crystallisation from aqueous sodium hydroxide, then separating in jagged yellow laths having a pearly lustre, m. p. 298° (Found : C, 52.0; H, 4.7; N, 7.7. $C_{16}H_{11}N_2S_2Na \cdot 3H_2O$ requires C, 51.6; H, 4.6; N, 7.5%); it gave the original mercapto-compound on acidification.

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) in 2*N*-sodium hydroxide (6 c.c.) diluted to 25 c.c. was treated with 50% glyoxal (1.5 c.c.) in water (5 c.c.). An intense purple colour appeared immediately, heat was evolved, and a sodium salt soon separated. The salt was suspended in hot water (100 c.c.) and acidified to give the free condensation product; more was obtained from the filtrate from the sodium salt (total yield 1.8 g.). The bisazomethine compound (VII) was practically insoluble in ethanol, acetic acid, dioxan, toluene, and other solvents but crystallised from pyridine-ethanol in sheaves of purple needles, m. p. 292–293° (decomp.) (Found : C, 55.0; H, 3.4. $C_{20}H_{14}N_4S_4$ requires C, 54.8; H, 3.2%). It was soluble in alcoholic ammonia to a purple solution which became deep blue in acetone, the sodium salt also giving a blue solution with acetone. The colour was observed also in pyridine but not in dioxan, ethanol, ethyl acetate, or diethylamine.

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.), acetic anhydride (10 c.c.), and 1 drop of concentrated sulphuric acid were refluxed for 3 minutes and solvent removed in a vacuum. The crystalline residue was dissolved in hot ethanol (15 c.c.). On cooling, the crystals (0.7 g.), m. p. 162–163°, were collected, and a second crop (1.5 g.), m. p. 148–158°, isolated from the mother-liquor (this material consisted mainly of the diacetyl derivative and on crystallisation from aqueous ethanol the m. p. rose considerably). The solid in the minimum of acetone-benzene (1 : 3) was chromatographed on alumina and eluted with 10% and ultimately with 90% acetone in benzene. The material from 10 fractions was substantially homogeneous (m. p. 244–247°). It was insoluble in hydrocarbons, chloroform, ethyl acetate, ether, or water, but soluble in hot ethanol, acetone, or acetic acid. 5-Acetamido-2-mercapto-4-phenylthiazole (XII) separated from ethanol in colourless needles, m. p. 244–245° (Found : C, 53.1; H, 4.0; N, 10.9. $C_{11}H_{10}ON_2S_2$ requires C, 52.8; H, 4.0; N, 11.2%), which dissolved immediately in alkali. In a larger preparation 5-amino-2-mercapto-4-phenylthiazole (30 g.) was heated to boiling with acetic anhydride (100 c.c.), and the clear solution poured into water (11.). The precipitated oil rapidly granulated and was dissolved in sufficient warm 2*N*-sodium hydroxide and precipitated with concentrated hydrochloric acid from a total volume of 21. The product (35.5 g.), after being washed and dried at 100°, had m. p. 244° (decomp.). The parent aminothiazole (IV)

(1 g.) was refluxed for 5 mins. with acetic anhydride (5 c.c.). On cooling, the solid was collected and washed with ether, more being obtained from the filtrate on adding light petroleum (total yield, 1.15 g.). 5-Diacetylamino-2-mercapto-4-phenylthiazole (XI) recrystallised best from acetic anhydride in prismatic needles, m. p. 166° (Found: C, 53.2; H, 4.2. $C_{13}H_{11}O_4N_2S_2$ requires C, 53.4; H, 4.1%); it dissolved (0.5 min.) in cold 2N-sodium hydroxide, the preceding monoacetyl derivative being recovered on acidification, and hydrolysis also took place slowly on exposure to air. The parent aminothiazole (IV) (2 g.) was warmed for 45 mins. at 100° with acetic anhydride (10 c.c.) containing a little sulphuric acid, and the solution finally refluxed for 3 mins. and evaporated in a vacuum. The residue crystallised and was recrystallised (yield 0.9 g.) from ethanol to give the triacetyl derivative (XIII) as prisms, m. p. 132° (Found: C, 54.0; H, 4.3; N, 8.5. $C_{15}H_{11}O_6N_2S_2$ requires C, 53.9; H, 4.2; N, 8.4%). This compound also reverted to the N-monoacetyl compound on mild hydrolysis.

5-Amino-2-mercapto-4-phenylthiazole (IV) (10 g.) in 2N-sodium hydroxide (20 c.c.) was stirred with chloroform (50 c.c.) and methyl sulphate (5 c.c.) dropped in during 5 mins. Acidification of the aqueous layer gave unchanged starting material (1 g.). Evaporation of the chloroform layer and addition of alcoholic hydrogen chloride gave 5-amino-2-methylthio-4-phenylthiazole hydrochloride, which crystallised from ethanol in magnificent, pale yellow needle clusters, m. p. 175° (decomp.) (Found: C, 46.3; H, 4.3; N, 10.6. $C_{10}H_{11}N_2S_2Cl$ requires C, 46.4; H, 4.3; N, 10.8%). The crude free base obtained from the chloroform solution above was mixed with a small excess of acetic anhydride; heat was evolved and the mixture solidified. 5-Acetamido-2-methylthio-4-phenylthiazole (IX) crystallised from ethanol in well-formed needles, m. p. 168° (Found: C, 54.9; H, 4.6; N, 10.4. $C_{12}H_{13}ON_2S_2$ requires C, 54.6; H, 4.6; N, 10.6%). The compound was still a base, affording a crystalline hydrochloride with hydrogen chloride in ethyl acetate.

In a larger methylation experiment (41.6 g. of aminomercapto-compound) the chloroform was evaporated and the semi-crystalline residue treated with ethyl acetate to give 5-amino-2-methylthio-4-phenylthiazole methosulphate (5.0 g.), which crystallised best from *tert*-butanol in long needles, m. p. 123° (Found: C, 41.0; H, 5.0; N, 8.0. $C_{12}H_{13}O_4N_2S_2$ requires C, 41.4; H, 4.6; N, 8.0%). The compound was water-soluble, and reaction with aqueous quinaldine methiodide containing 1 equiv. of sodium hydroxide gave a deep purple precipitate; no colouration was obtained with glyoxal. The substance was biologically inactive towards *Staph. aureus* in 0.2% phosphate buffer (pH 7). The corresponding *picrate* crystallised from acetic acid in needles, m. p. 202° (Found: C, 44.3; H, 3.4; N, 14.9. $C_{11}H_{10}O_7N_2S_2$ requires C, 43.9; H, 3.2; N, 15.0%). The ethyl acetate filtrate (above) was evaporated, and the residue in ether run on to an alumina column and developed with 20% ether in light petroleum. The eluates yielded 5-amino-2-methylthio-4-phenylthiazole (VIII), which crystallised from light petroleum (b. p. 80–100°) in colourless needles, m. p. 70–71° (Found: C, 54.0; H, 5.0; N, 12.8. $C_{10}H_{10}N_2S_2$ requires C, 54.0; H, 4.5; N, 12.6%).

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) was refluxed with methyl iodide (1.5 g.) in ethanol (10 c.c.) for 0.5 hour. On cooling, a mass of pale needles separated (2.7 g.), which recrystallised from ethanol to give 5-amino-2-methylthio-4-phenylthiazole hydriodide, m. p. 172° (decomp.) (Found: C, 34.5; H, 3.5. $C_{10}H_{11}N_2S_2I$ requires C, 34.3; H, 3.14%).

5-Acetamido-2-mercapto-4-phenylthiazole (XII) (34 g.) was refluxed with methyl iodide (20 g.) in ethanol (200 c.c.) for 10 minutes, the reaction being exothermic. Pyridine (10 c.c.) was added, and the mixture cooled to yield 5-acetamido-2-methylthio-4-phenylthiazole (IX) (37 g.), m. p. 162–210°; dilution of the filtrate with water gave a second crop (8.5 g.), m. p. 167°. The combined crops were recrystallised from ethanol (250 c.c.) to yield the pure thiazole above, m. p. 168°.

α -Aminobenzyl cyanide (2.6 g.), benzyl chloride (2.5 g.), and carbon disulphide (1.5 g.) were kept at room temperature in pyridine (10 c.c.) for 18 hours. The solvent was evaporated in a vacuum, and the syrupy residue treated with water (20 c.c.) and ether (20 c.c.); a small quantity of 5-amino-2-mercapto-4-phenylthiazole separated and was removed by filtration. The ether was washed successively with 2N-sodium hydroxide (20 c.c.), 2N-hydrochloric acid (10 c.c.), and water (20 c.c.) and dried and evaporated to yield 5-amino-2-benzylthio-4-phenylthiazole, m. p. 107° (Found: C, 65.0; H, 5.0; N, 9.2; S, 21.4. $C_{16}H_{14}N_2S_2$ requires C, 64.4; H, 4.7; N, 9.2; S, 21.5%). The compound crystallised best from cyclohexane, and lost benzylthiol on treatment with aqueous alkali. It readily condensed with glyoxal to give a scarlet Schiff's base and could be diazotized in acid solution.

5-Amino-2-methylthio-4-phenylthiazole hydrochloride (2.5 g.), dissolved in acetic acid (25 c.c.) containing concentrated sulphuric acid (2 c.c.), was cooled in a freezing mixture, and treated during 5 minutes with N-sodium nitrite (10 c.c.). After standing in ice for a further 10 minutes, the diazotised base was added to a solution of β -naphthol (1.4 g.) in ethanol (40 c.c.) and water (10 c.c.) containing saturated aqueous sodium acetate (10 c.c.), and the precipitated dye collected. Extraction with hot ethanol followed by solution in warm benzene and precipitation with light petroleum (b. p. 40–60°) gave 2-methylthio-4-phenylthiazole-5-azo- β -naphthol (1.5 g.), which crystallised from ethyl acetate in long red needles, m. p. 170–171°, and gave an intense blue solution in concentrated sulphuric acid (Found: C, 63.2; H, 4.2; N, 11.3. $C_{20}H_{15}ON_3S_2$ requires C, 63.6; H, 4.0; N, 11.1%).

5-Amino-2-methylthio-4-phenylthiazole (VIII) (1.7 g.) in cold ethanol (30 c.c.) was treated with 50% glyoxal (3 c.c.) in ethanol (10 c.c.). A scarlet colour and crystalline precipitate appeared within 20 secs. The solution was heated to boiling and filtered hot (yield, 0.7 g.). The *azomethine* compound was insoluble in ethanol, acetic acid, or ethyl acetate, moderately soluble in hot chloroform, benzene, or toluene, and crystallised from benzene containing a little light petroleum in needles, m. p. 242–243° (decomp.). The compound appeared to form a labile brown hydrochloride, dissolved in concentrated sulphuric acid to a purple solution, and was apparently stable to boiling 2N-sodium hydroxide.

In another preparation of this and other methylated Schiff's bases equivalent proportions of the carbonyl compound and 5-amino-2-methylthio-4-phenylthiazole hydrochloride were mixed in cold methanol, and the condensation product crystallised in almost quantitative yield. The results are summarised in the following table. This method was also most convenient for preparing the mercapto-Schiff's bases from 5-amino-2-mercapto-4-phenylthiazole hydrochloride, and the last two entries in the table are examples of its use.

Carbonyl component.	M. p. and colour.	Recryst. from : *	Formula.	Analysis.					
				Found, %.			Required, %.		
				C.	H.	N.	C.	H.	N.
Benzaldehyde	119°, yellowish-green	A	C ₁₇ H ₁₄ N ₂ S ₂	65.2	4.4	8.4	65.8	4.5	9.0
Cinnamaldehyde	143°, bronze	B	C ₁₉ H ₁₆ N ₂ S ₂	68.5	5.8	8.1	67.9	4.8	8.3
Glyoxal	241—242°, deep red	C	C ₂₂ H ₁₈ N ₄ S ₄	66.8 57.0	4.6 4.2	12.2	66.8 56.7	4.6 3.9	12.0
Phenanthraquinone	187—188°, brown, green reflex	D	C ₂₄ H ₁₄ ON ₂ S ₂	69.5	4.0	6.5	69.9	3.9	6.8
Isatin	230°, scarlet-red	C	C ₁₈ H ₁₃ ON ₂ S ₂	61.9	3.9	11.6	61.5	3.7	12.0
Alloxan	288°, red	E	C ₁₄ H ₁₀ O ₃ N ₄ S ₂	49.2 48.0	3.1 2.8	16.4	48.6	2.9	16.2
Phenanthraquinone (SH)	211°, deep purple	—	C ₂₃ H ₁₄ ON ₂ S ₂	69.0	3.8	6.4	69.3	3.5	7.0
Isatin (SH)	311°, purple, coppery lustre	E	C ₁₇ H ₁₁ ON ₃ S ₂	60.4	3.7	12.1	60.5	3.3	12.5

* A = ethanol; B = acetic acid; C = benzene; D = ethyl acetate; E = pyridine.

5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) and *p*-nitrosodimethylaniline (5 g.) were warmed in pyridine (25 c.c.) to initiate the exothermic reaction. Evaporation and addition of water-ethanol (1 : 4, 40 c.c.) gave red-brown crystals which were recrystallised in similar manner or from light petroleum and then had m. p. 92°; this is probably the *quinoneimine* (X) (Found : C, 77.1; H, 7.4. C₂₂H₁₂N₄ requires C, 77.5; H, 6.4%). On rapid treatment with ethanolic hydrogen chloride a labile hydrochloride was obtained, but longer treatment (at room temp. for 10 mins.) followed by addition of ether gave *p*-aminodimethylaniline dihydrochloride, m. p. 208° (decomp.) (lit. m. p. 218°) (Found : C, 46.6; H, 6.9; N, 12.7. Calc. for C₈H₁₀N₂Cl₂ : C, 46.0; H, 6.7; N, 13.4%). It gave known colour reactions with ferric chloride, sodium nitrite, sodium nitroprusside, hydrogen peroxide, alkaline ferricyanide, and iodine in potassium iodide, and the methylene-blue reaction with hydrogen sulphide followed by ferric chloride.

Oxidation Experiments.—5-Amino-2-mercapto-4-phenylthiazole (IV) was oxidised in aqueous alkali under a variety of conditions, forming an insoluble, red, crystalline, sodium salt, and a number of other more complex green oxidation products which have not been investigated. Hydrogen peroxide, oxygen, potassium ferricyanide, sodium nitroprusside, and benzoquinone all gave red and green products, though the proportion seemed to vary with the oxidising agent employed. None of the simple disulphide was isolated in these experiments, though there is evidence that it was formed in acid solution.

In a typical large-scale experiment, the aminothiazole (15 g.) was dissolved in 2*N*-sodium hydroxide (40 c.c.), and oxygen passed through the solution for 16 hours. The red needle crystals (1.8 g.) which were precipitated were filtered off, washed with a little water and dried. They decomposed at 277—278° and contained sodium. Solution in ethanol, acetone, ethyl acetate, dioxan, or pyridine was very ready, and the material could be crystallised from these solvents by adding ether or light petroleum. Crystallisation was best effected, however, from warm water, in which the salt was readily soluble. In all but acetone and pyridine the solutions were deep red, but in these two solvents the reagent colour was very similar to the rhodamines, showing also a violet fluorescence (cf. behaviour of sodium salt of glyoxal Schiff's base). Addition of other metallic ions to the aqueous sodium salt solution caused precipitation of crystalline and highly coloured metallic derivatives; e.g., the barium salt melted at 267—270° and crystallised beautifully from hot aqueous ethanol. Acidification of the sodium salt caused precipitation of the free acid (see below) as light orange needles, m. p. 241°. 5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) in 2*N*-sodium hydroxide (12 c.c.) was treated with acetylsulphanil chloride (2 g.), producing an intense purple colour which later became green. After being shaken for 1 hour at room temperature, the mixture was filtered, and the insoluble material (0.95 g.) purified by recrystallisation from warm sodium carbonate solution, forming deep red needles, m. p. 268—269°, identical with the above sodium salt.

The sodium salt (1.8 g.) was dissolved in hot water (200 c.c.) and filtered from a little insoluble material. Sodium hydrogen carbonate solution (20 c.c.) was added, followed by chloroform (100 c.c.), and methyl sulphate was dropped into the well-stirred mixture until the intense colour had passed from the aqueous to the organic layer. The mixture was filtered from some orange material (substance A) which had separated during the reaction and the chloroform was separated, washed, dried, and evaporated to yield a mass of dark crystals. These were washed with ether which removed most of the colour, leaving a yellow substance which crystallised well from hot ethanol in needles, m. p. 128° [Found : C, 64.5; H, 3.9; N, 11.7; M (Rast), 306. C₂₀H₁₆ON₂S₄ requires C, 64.2; H, 3.7; N, 11.8%; M, 710]. Light absorption (chloroform) : $\lambda_{\max.} = 265, 282, 327, 450 \text{ m}\mu$; $E_{1\%}^{1\text{cm.}} = 525, 525, 320, 820$.

Substance A melted at 239—240°, and was identical with the free acid. It was insoluble in both hot and cold water, ether, alcohol, acetic acid, and toluene, sparingly soluble in hot ethyl acetate and chloroform, and readily soluble in acetone, dioxan, and pyridine on gentle warming. However, crystallisation proved difficult; use of mixed solvents in the cold caused either too rapid precipitation or none, and prolonged heating with acetic acid or aqueous dioxan caused decomposition into alkali-insoluble materials, and yellow materials soluble or insoluble in alkali according to conditions. These degradation products were not further investigated. The compound crystallised best from a large volume of hot chloroform in small orange needles, m. p. 239—240° (Found : C, 62.9; H, 3.4; N, 12.1. C₂₀H₁₆ON₂S₄ requires C, 63.3; H, 3.3; N, 12.3%). Light absorption (dioxan) : $\lambda_{\max.} = 223, 260, 270, 315, 450 \text{ m}\mu$. $E_{1\%}^{1\text{cm.}} = 400, 500, 400, 400$.

5-Amino-2-mercapto-4-phenylthiazole (IV) (10 g.) and Raney nickel (24 g.) were suspended in ethanol (120 c.c.) and the mixture heated to boiling, after which the heat of reaction caused spontaneous refluxing. When reaction was complete the mixture was cooled, filtered from nickel sulphide, and evaporated in a vacuum. The brown semicrystalline residue possessed an amine-like odour and gave an intense green fluorescence in ethanol, probably due to small amounts of 2 : 2'-bisthiazoles (Karrer and Sanz, *Helv. Chim. Acta*, 1944, 27, 619). It was dissolved in benzene and chromatographed on alumina; development and elution with this solvent gave, on evaporation, 5-amino-4-phenylthiazole, m. p. 135–136°. Continued elution with 20% acetone in benzene yielded a further quantity of the aminothiazole, best isolated as the hydrochloride. This substance did not give a red Schiff's base with methanolic glyoxal. 5-Acetamido-2-mercapto-4-phenylthiazole (XII) (0.5 g.) and Raney nickel (1.2 g.) were suspended in ethanol (20 c.c.), and the mixture refluxed for 10 minutes. Nickel sulphide was removed by filtration, and evaporation in a vacuum gave 5-acetamido-4-phenylthiazole, m. p. 147–148°. The reaction was cleaner than with the parent amine. The benzaldehyde Schiff's base of 5-amino-2-mercapto-4-phenylthiazole (1.0 g.) and Raney nickel (3 g.) were refluxed in ethanol (20 c.c.) for 15 minutes. After filtration and evaporation in a vacuum a rather poor yield of 5-amino-4-phenylthiazole hydrochloride, m. p. 216° (decomp.), was obtained by treating the residue with ethereal hydrogen chloride containing a little ethanol. The acetone Schiff's base of 5-amino-2-mercapto-4-phenylthiazole (V) (0.5 g.) and Raney nickel (3 g.) were refluxed in ethanol (15 c.c.) for 15 minutes. Filtration and evaporation gave, on rubbing with benzene, 5-amino-4-phenylthiazole m. p. 135–136°.

5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) was moistened with ethanol and boiled with 2N-hydrochloric acid (50 c.c.) for 1.5 hours. No hydrogen sulphide was produced, but an oily liquid was formed which was distilled out and collected in methanol containing some α -aminobenzyl cyanide. The solution, on standing for a day, deposited yellow crystals of 5-amino-2-mercapto-4-phenylthiazole (IV), m. p. 261°, together with a small quantity of red, alkali-soluble crystals, m. p. 272–273°. Essentially, therefore, the sulphur is split out as carbon disulphide. The hydrolysate was filtered from some insoluble material (0.7 g.; a mixture of unreacted thiazole and an orange-brown substance) and evaporated to dryness. The residue was treated with acetone to give colourless rods of α -aminophenylacetic acid hydrochloride (2.7 g.). Recrystallised from 18% hydrochloric acid it had m. p. 212° (decomp.); mixed m. p. with authentic material, 209° (decomp.). Treatment with potassium acetate solution gave the free base, subliming at 285–290°; authentic α -aminophenylacetic acid sublimed at 281–283°.

5-Amino-2-mercapto-4-phenylthiazole (IV) (20 g.) was boiled with 2N-sodium hydroxide (100 c.c.) for 1 hour. The solution, which now failed to give a scarlet Schiff's base with glyoxal, was diluted with water (600 c.c.), and the product precipitated by 2N-hydrochloric acid (200 c.c.) was extracted with boiling acetic acid (300 c.c., 300 c.c., 200 c.c.). The orange residue (4 g.) was insoluble in all common solvents except pyridine and was crystallised from alcoholic potash by addition of acetic acid to give 1' : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV), m. p. 270–271° (decomp.) (Found : C, 51.8; H, 3.15; N, 13.6. $C_{18}H_{14}N_4S_4$ requires C, 52.2; H, 3.4; N, 13.5%). The acetic acid filtrates were cooled to 0° and the 2 : 4-dithio-5-phenylhydantoin (XIV) which separated (10.5 g.) was recrystallised rapidly from acetic acid, forming colourless clusters of stout needles, m. p. 264–265° (decomp.) (Found : C, 51.9, 52.5; H, 4.3, 3.8. $C_8H_8N_2S_2$ requires C, 51.9; H, 3.9%). This substance readily darkened on exposure to air or undue heating in solvents. It was soluble in pyridine and dioxan on gentle warming, moderately soluble in hot acetic acid, sparingly soluble in hot ethanol, and insoluble in other common solvents.

5-Amino-2-mercapto-4-phenylthiazole (IV) (1 g.) was boiled gently in aqueous ammonia (d 0.880) for 2 hours, a sufficient concentration of ammonia being maintained to keep the thiazole in solution. The ammonia was then boiled off, and after filtration from unreacted mercaptothiazole, the solution was acidified to yield 2 : 4-dithio-5-phenylhydantoin (XIV), m. p. 264–265° (decomp.). 5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) was refluxed in pyridine (20 c.c.) for 15 minutes; some hydrogen sulphide was evolved and the solution became deep red. On cooling, a mass of deep red crystals was produced, which could be recrystallised from pyridine, and melted at about 75°. On exposure to air for 10 minutes, or treatment with ethanol or water, the material fell to an insoluble orange powder, m. p. 270–271°, identical with 1' : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV). The same result was obtained when 2 : 4-dithio-5-phenylhydantoin (XIV) was substituted for the aminothiazole in the above experiment. The deep red crystals were not produced, however, when a saturated pyridine solution of the bisdithiohydantoin (XV) was cooled. 5-Amino-2-methylthio-4-phenylthiazole hydriodide (1 g.) was refluxed with 2N-sodium hydroxide (20 c.c.) for 0.5 hour. The solution was filtered from a little unsaponified material and acidified with concentrated hydrochloric acid. Methylthiol was evolved and yellow granular crystals of 4-thio-5-phenylhydantoin (XVI) were precipitated, m. p. 259–260° (decomp.) (Johnson and Chernoff, *loc. cit.*, give m. p. 259°, decomp.); mixed m. p. with the dithiohydantoin (XIV) 244° (decomp.).

2 : 4-Dithio-5-phenylhydantoin (XIV) (2 g.) and Raney nickel (6 g.) were suspended in ethanol (50 c.c.), and the mixture refluxed for 10 minutes. After filtration from nickel sulphide and evaporation to dryness, the residue was extracted with ether to yield, on removal of solvent, 5(4)-phenyliminazole (XVII) (0.5 g.) (Found : C, 75.0; H, 5.8. Calc. for $C_8H_8N_2$: C, 75.0; H, 5.6%), which crystallised from benzene in plates, m. p. 133–134° (Pinner, *Ber.*, 1902, 35, 4135, gives m. p. 128–129°). 1' : 5-Bis-(2 : 4-dithio-5-phenylhydantoin) (XV) (2.5 g.) was refluxed in ethanol (50 c.c.) with Raney nickel (6 g.) for 0.5 hour. Filtration and evaporation yielded 5(4)-phenyliminazole (XVII), m. p. 133–134°, extracted from the residue with ether.

5-Phenylhydantoin (1.2 g.) (Lehmann, *Ber.*, 1901, 34, 372) was boiled in tetralin (20 c.c.) with phosphorus pentasulphide (3 g.) for 2 hours. The hot solvent was decanted from the lower oily layer which dissolved in warm 2N-sodium hydroxide (50 c.c.), and yielded 5(4)-phenyliminazole (XVII) (0.6 g.), m. p. 132–133° (mixed m. p. with product from Raney nickel desulphurisation of the dithiohydantoin, 133–134°), on cooling.

5-Amino-2-mercapto-4-phenylthiazole (IV) (20 g.) was boiled with 2N-sodium hydroxide (250 c.c.) until the solution no longer gave an intense red colour with aqueous glyoxal (0.5 hr.). Chloroform

(100 c.c.) and benzyl chloride (25 g.) were then added, and the mixture shaken for 4 hours. The plates, m. p. 108°, which had separated (28 g.) were filtered off and washed with chloroform. This substance was a sodium salt, recrystallisation of which from acetic acid yielded 2 : 4-dithio-5-phenyl-1(or 3)-benzylhydantoin in needles, m. p. 194° (Found : C, 64.2; H, 4.6; N, 9.2. $C_{16}H_{14}N_2S_2$ requires C, 64.2; H, 4.7; N, 9.4%). Light absorption (ethanol) : λ_{\max} 277 m μ , $E_{1\%}^{1\text{cm}}$ = 750. The above sodium salt (16 g.) was dissolved in warm ethanol (50 c.c.), and benzyl chloride (6.5 g.) added. After standing at room temperature for 1 hour the sodium chloride was filtered off, and evaporation of the filtrate to small bulk in a vacuum gave a mass of colourless needles. 2 : 4-Dithio-5-phenyl-1 : 3-dibenzylhydantoin crystallised from chloroform-light petroleum (b. p. 40–60°) in needles, m. p. 114° (Found : C, 69.6; H, 5.2; N, 7.4; S, 16.7. $C_{22}H_{20}N_2S_2$ requires C, 71.1; H, 5.2; N, 7.2; S, 16.5%). Light absorption (chloroform) : λ_{\max} 277 m μ , $E_{1\%}^{1\text{cm}}$ 390. The substance was recovered unchanged after refluxing for 0.5 hour in acetic anhydride. A little of the dibenzyl derivative was dissolved in acetic acid, and the crystalline hydrochloride precipitated by addition of a few drops of ethanolic hydrogen chloride. 2 : 4-Dithio-5-phenyl-1 : 3-dibenzylhydantoin hydrochloride crystallised from acetic acid in colourless needles, m. p. 168–170° (Found : C, 64.6; H, 5.1; N, 6.6; S, 14.7. $C_{22}H_{20}N_2S_2 \cdot HCl$ requires C, 65.0; H, 5.0; N, 6.6; S, 15.1%). It was soluble in ethanol and insoluble in acetone.

1' : 5-Bis-(2 : 4-dithio-5-phenylhydantoin) (XV) (0.5 g.) was refluxed with 2N-sodium hydroxide (10 c.c.) for 1 hour. Acidification yielded 2 : 4-dithio-5-phenylhydantoin (XIV) (0.4 g.), m. p. 267–268° (decomp.); (XIV) was stable in alkali. 2 : 4-Dithio-5-phenylhydantoin (2 g.) was boiled with 50% sulphuric acid (25 c.c.) for 24 hours, the material initially turning orange with simultaneous evolution of sulphur dioxide. The mixture was diluted with water, and the insoluble crystals, m. p. 261° (decomp.), collected. After treatment with 2N-sodium hydroxide and removal of a little insoluble material, m. p. 257–261°, acidification gave orange 1' : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV), m. p. 270–271° (decomp.).

A warm saturated solution of the dithiohydantoin (XIV) in ethanol was treated with iodine in ethanol; immediate decolourisation occurred and 1' : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV) was precipitated, m. p. 272° (decomp.). Ferric chloride added to an acetic acid solution gave a similar result. Hydrogen peroxide in ethanol gave an insoluble product, m. p. 271–272° (decomp.), which, however, was not identical with 1' : 5-bis-(2 : 4-dithio-5-phenylhydantoin). When an ethanolic solution of 2 : 4-dithio-5-phenylhydantoin was refluxed, the bis-compound (XV) was slowly deposited owing to aerial oxidation.

Reactions with α -Aminopropionitrile.—Acetaldehyde-ammonia (73 g.) was added in portions during 2 hours to ice-cold anhydrous hydrogen cyanide (48 c.c.), and the mixture kept for 2 hours at room temperature and distilled at 12–15 mm. (Delépine, *Bull. Soc. chim.*, 1903, **29**, 1184). Two main fractions were obtained, (A) b. p. 65–75°, and (B), b. p. 115–125°, as well as smaller intermediate fractions. Fraction (A), which is essentially α -aminopropionitrile (2.1 g.), was kept with carbon disulphide (2.3 g.) in ethanol (25 c.c.) for 2 days. 2 : 4-Dithio-5-methylhydantoin (3 g.) separated, m. p. 224° (decomp.), and was crystallised by solution in aqueous ammonia (d 0.880), dilution with 50% ethanol, and precipitation with 2N-hydrochloric acid. The compound was insoluble in common solvents except pyridine, and readily darkened on exposure to light and air. It was soluble in aqueous alkali and the solution gave a red colour with sodium nitroprusside but not with glyoxal. In the presence of acetaldehyde, formation of dithiohydantoin in the above reaction was completely inhibited and the acetaldehyde Schiff's base of the corresponding thiazole (see below) was obtained, though in poor yield.

Fraction (B), diluted with ethanol, was kept overnight with excess of carbon disulphide, and a mass of colourless needles of the acetaldehyde Schiff's base of 5-amino-2-mercapto-4-methylthiazole, m. p. 203° (decomp.), separated (Found : C, 42.1; H, 4.8; N, 16.1; S, 37.2. $C_6H_8N_2S_2$ requires C, 41.9; H, 4.7; N, 16.3; S, 37.2%). The compound was soluble in hot ethanol, ethyl acetate, and acetic acid, and in cold dioxan and pyridine. It readily darkened on exposure to light or on heating in solvents. The Schiff's base was readily soluble in aqueous alkali, and on warming, acetaldehyde was evolved; warm dilute acids also liberated acetaldehyde. When ethanolic hydrogen chloride was added to a solution of the Schiff's base in warm ethyl acetate, 5-amino-2-mercapto-4-methylthiazole hydrochloride, m. p. 197° (decomp.), was rapidly precipitated (Found : C, 26.6; H, 4.1; N, 14.8. $C_6H_8N_2S_2 \cdot Cl$ requires C, 26.3; H, 3.8; N, 15.3%). The compound was insoluble in acetic acid, acetone, and ethanol, soluble in methanol and water, and was best crystallised from methanol and ether. It darkened on exposure to light, and did not yield a free base on treatment with aqueous sodium hydrogen carbonate; treatment of a methanolic or aqueous solution of the above hydrochloride with aqueous glyoxal gave an immediate scarlet precipitate.

α -Aminopropionitrile hydrochloride (5.3 g.) (Dubsy, *Ber.*, 1916, **49**, 1048) was suspended in ethanol (25 c.c.) containing a little phenolphthalein and titrated to neutrality with N-ethanolic sodium ethoxide. After filtration from sodium chloride, the mixture was set aside over-night at 0° with carbon disulphide (4 c.c.). 2 : 4-Dithio-5-methylhydantoin (1.1 g.), m. p. 223° (decomp.), separated, and addition of ethereal hydrogen chloride to the filtrate gave 5-amino-2-mercapto-4-methylthiazole hydrochloride (1.1 g.), m. p. 197° (decomp.).

Reaction with Ethyl Aminocynoacetate.—An ethereal solution of the ester (see Part I, *loc. cit.*) was kept overnight at 0° with excess of carbon disulphide. Extraction and crystallisation of the residue from ethanol yielded colourless barrel-shaped tablets of 5-amino-2-mercapto-4-carbethoxythiazole, m. p. 182–183° (decomp.) (Found : C, 35.7; H, 4.0; N, 13.4. $C_8H_8O_2N_2S_2$ requires C, 35.3; H, 3.9; N, 13.7%). The compound contains a diazotisable group but did not give a colour with glyoxal. The above compound (2 g.) was suspended in ethanol (30 c.c.) with Raney nickel (6 g.) and refluxed for 15 minutes. Filtration of the intensely blue fluorescent solution and evaporation yielded 5-amino-4-carbethoxythiazole, m. p. 163° after crystallisation from ethyl acetate, undepressed by the material described in the preceding paper.

5-Amino-2-mercapto-4-carbethoxythiazole (1.0 g.) was refluxed with methyl iodide (1.0 g.) in ethanol (5 c.c.) for 3 minutes, and the plates (1.5 g.) which separated on cooling recrystallised from methanol and

ether to give 5-amino-2-methylthio-4-carbethoxythiazole hydriodide, m. p. 164–165° (decomp.) (Found: N, 8.1. $C_7H_{11}O_2N_2S_2$ requires N, 8.1%). Treatment with aqueous sodium hydrogen carbonate readily yielded the corresponding base, which crystallised from aqueous ethanol in long needles, m. p. 108° (Found: C, 38.8; H, 5.1; N, 13.1; S, 29.4. $C_7H_{10}O_2N_2S_2$ requires C, 38.5; H, 4.6; N, 12.8; S, 29.4%).

Reaction with Carbon Dioxide.— α -Aminobenzyl cyanide (1 g.) was dissolved in ethanol (30 c.c.), and a slow stream of carbon dioxide passed through the solution overnight. The flocculent precipitate was recrystallised from acetic acid to give α -cyano- α' -carbamyldibenzylurea (XVIII; R = H, R' = Ph), m. p. 224° (decomp.) (Found: C, 66.0; H, 5.3. $C_{17}H_{16}O_2N_4$ requires C, 66.2; H, 5.2%). The compound was only slowly attacked by boiling dilute acids and alkalis.

Light absorption of thiazoles,



Substituents:			Solvent.	$\lambda_{max.}$	$E_{1\%}^{1cm.}$
2.	4.	5.			
SH	Ph	NH ₂	Dioxan	281 290 300	460
			Aq. NaOH	223 306 223	680 660 980
SAC	Ph	NAC ₂	CHCl ₃	290 (inflexion) 242	195 660
SH	Ph	NAC ₂	CHCl ₃	235 282 291 306	560 420 360
SH	Ph	NHAc	Dioxan	228 281 290 308 323	700 510 410 310
SMe	Ph (hydrochloride)	NH ₂	MeOH	223 281 290 308	560 390 370
SH	CO ₂ Et	NH ₂	Dioxan	282 291 306 320 336	490 480 420 370 300
SMe	Ph (methosulphate)	NH ₂	EtOH	228 242 350	220 165 280
SMe	Ph	NHAc	CHCl ₃	235 282 290 300 308	600 460 490
SNa	Ph	N:CHPh	EtOH	219 265 282 290 428	600 650 600 500 625
SH	Ph	N:CMcPh	Dioxan	255 328 401 267 280 365	875 240 400 535 440 240
SH	Ph	N:CMc ₂	Dioxan	290 352 260 372	500 230 650 300
SMe	Ph	N:CH-CH:N (bis-azomethine)	CHCl ₃	265 281 290 498	520 600 715

inflexions

inflexions

after 1 day

after 1 day

We thank I.C.I. Ltd. (Dyestuffs Division) for gifts of chemicals, and Dr. E. A. Braude for the absorption spectra.

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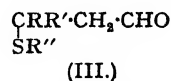
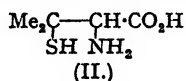
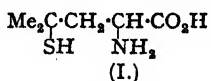
[Received, January 23rd, 1947.]

320. *Syntheses of Some Amino-acids, including Methionine.*

By J. R. CATCH, A. H. COOK, A. R. GRAHAM, and SIR IAN HEILBRON.

Methyl-, ethyl-, and benzyl-thiol readily combined with acraldehyde in presence of organic bases to give β -methyl-, -ethyl-, and -benzyl-thiopropaldehydes, which were satisfactorily converted by the Strecker reaction into methionine, ethionine, and S-benzylhomocysteine respectively. Similar reactions employing benzylthiol with crotonaldehyde or β -methylcrotonaldehyde led to the corresponding α -amino- γ -benzylthio-acids of which the second was debenzylated to α -amino- γ -mercapto- γ -methyl-*n*-valeric acid. In accordance with this formulation, the acid did not behave like a substituted cysteine but gave thiazans (*i.e.*, 6-membered ring compounds) by condensation with carbonyl compounds. Some of the above amino-acids were also obtained by indirect hydrolysis of the corresponding nitriles *via* heterocyclic intermediates.

THIS work was carried out in connection with the synthesis of α -amino- γ -mercapto- γ -methyl-*n*-valeric acid (I). This acid is of interest in view of its relationship to penicillamine (II), a degradation product of the various naturally occurring penicillins, and therefore presents the possibility of obtaining analogues of the natural antibiotics.



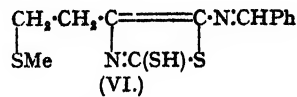
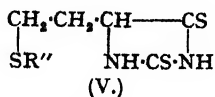
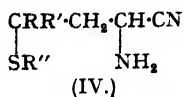
Compounds which might have provided the closest models for the synthesis of (I) were methionine and homocysteine. However the syntheses of these acids which have hitherto been considered most practicable would require, when applied to (I), intermediates of doubtful accessibility. An obvious route to methionine, the Strecker reaction applied to β -methylthiopropaldehyde (III; R, R' = H; R'' = Me), has been explored by Barger and Coyne (*Biochem. J.*, 1928, 22, 1420) and rejected as a useful method because of poor yields. Despite this circumstance it seemed worth while exploring the possibilities of working with the analogue (III; R, R' = Me; R'' = H or other group).

The aldehyde (III; R, R' = H; R'' = Me) has previously been obtained (Barger and Coyne, *loc. cit.*) from β -chloropropaldehyde diethylacetal *via* the β -methylthioacetal, but direct addition of thioacetic acid or thiols to $\alpha\beta$ -unsaturated aldehydes offered an improved route. Kaneko and Mii (*J. Chem. Soc. Japan*, 1938, 59, 1382; *C.A.*, 1939, 33, 2106), and Rothstein (*J.*, 1940, 1560) have described the addition of methyl- and ethyl-thiol respectively to acraldehyde, but the conditions employed by the first-mentioned authors are obscure and the yield recorded for the second addition is poor. It has now been found that thioacetic acid readily adds to acraldehyde, crotonaldehyde, and β -methylcrotonaldehyde to give satisfactory yields of β -acetylthio-propaldehyde, -*n*-butaldehyde, and -isovaleraldehyde (III; R, R' = H; R = H, R' = Me; R, R' = Me respectively, R'' = Ac); these formulations are based on analogy with additions of thiols (see below) where there can be no doubt of the direction of addition. Meanwhile, similar reactions with thiols were found to proceed equally readily, and closer attention was paid to them in view of the greater probability of cleaner transformations at later stages.

Methyl- and ethyl-thiols were found to react quickly with acraldehyde at 0° in presence of a catalytic quantity of a strong base such as triethylamine to give β -methylthio- and β -ethylthio-propaldehyde (III; R, R' = H; R'' = Me, Et, respectively) in good yield. In similar fashion benzylthiol and the appropriate $\alpha\beta$ -unsaturated aldehyde afforded β -benzylthio-propaldehyde, -*n*-butaldehyde, and -isovaleraldehyde (III; R, R' = H; R = H, R' = Me; R, R' = Me respectively, R'' = CH₂Ph). All these aldehydes were characterised as their dinitrophenylhydrazones.

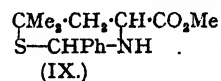
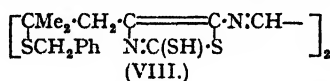
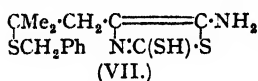
β -Methylthiopropaldehyde was converted by anhydrous hydrogen cyanide followed by ammonia into α -amino- γ -methylthio-*n*-butyronitrile (IV) (R, R' = H, R'' = Me) which was more conveniently isolated as its oxalate than as its hydrochloride. In the same way the homologous nitrile (IV; R, R' = H, R'' = Et) was obtained, also as its oxalate, and the

above-mentioned benzylthioaldehydes were similarly converted into the nitriles (IV; $R'' = \text{CH}_2\text{Ph}$; $R, R' = \text{H}$; $R = \text{H}, R' = \text{Me}$; $R, R' = \text{Me}$), isolated as their *hydrochlorides*.



Facile hydrolysis of certain α -amino-nitriles has been effected (Cook, Heilbron, and Levy, in the press) by first allowing them to react with carbon disulphide and refluxing the resulting 5-amino-2-mercaptothiazoles with dilute mineral acids, and the behaviour of some of the present α -amino-nitriles under these conditions was therefore investigated. α -Amino- γ -methylthio-*n*-butyronitrile and carbon disulphide gave 5- β -methylthioethylthiohydantoin (V) ($R'' = \text{Me}$) directly, though the anticipated 5-amino-2-mercapto-4- β -methylthioethylthiazole could be obtained as its *benzylidene* derivative (VI) by carrying out the condensation in presence of benzaldehyde (Cook, Heilbron, and Levy, *loc. cit.*). The nitrile (IV; $R, R' = \text{H}$; $R'' = \text{Et}$) similarly afforded 5-ethylthioethylthiohydantoin (V; $R'' = \text{Et}$). Hydrolysis of (V; $R'' = \text{Me}$) and of (VI) yielded methionine as was anticipated, but in these instances there was no advantage in proceeding *via* the heterocyclic compounds for methionine could be obtained in satisfactory yield by direct hydrolysis of the appropriate nitrile with boiling hydrochloric acid. It is noteworthy that by the steps outlined above methionine was obtained from acraldehyde in an overall yield of 29%, the process thus appearing much superior to earlier preparations. Ethionine was obtained similarly in equally satisfactory yield.

Two of the above α -aminobenzylthio-nitriles (IV; $R'' = \text{CH}_2\text{Ph}$; $R = \text{H}, R' = \text{H}$ or Me) were hydrolysed similarly without difficulty to give *s*-benzylhomocysteine and α -amino- γ -benzylthio-*n*-valeric acid respectively. The third α -aminobenzylthio-nitrile (IV) ($R'' = \text{CH}_2\text{Ph}$; $R, R' = \text{Me}$) was however converted into the corresponding α -amino-acid only in poor yield by direct hydrolysis. It was fortunate that in this case reaction with carbon disulphide under selected conditions gave not a dithiohydantoin but 5-amino-2-mercapto-4- β -benzylthioisobutylthiazole (VII). Unlike the previous dithiohydantoins, compound (VII) was not only pseudoacidic but was also basic and condensed easily with glyoxal in the characteristic manner of 5-amino-



2-mercaptothiazoles to give the *bisazomethine* derivative (VIII). The thiazole (VII) could be hydrolysed without difficulty and thus satisfactorily afforded α -amino- γ -benzylthio- γ -methyl-*n*-valeric acid. The benzyl group was removed from the latter compound by means of sodium in liquid ammonia to give α -amino- γ -thiol- γ -methyl-*n*-valeric acid (I).

The direction of addition of methyl- and ethyl-thiol to acraldehyde is clear from the eventual emergence of methionine and ethionine. That similar additions of benzylthiol take place in a comparable direction to that postulated above seems certain in that the amino-acid formulated as (I) failed to give the indigo-blue colour with ferric chloride which is characteristic of α -amino- β -thiol-acids such as cysteine and its homologues. The acid (I) still however condensed easily with carbonyl compounds, for example giving with benzaldehyde 4-carbomethoxy-6 : 6-dimethyl-2-phenylthiazan (IX) by simultaneous esterification.

It was at first thought that the amine corresponding to the amino-acid (I) might be more easily accessible and worthy of study. To this end β -benzylthio-*n*-butaldehyde and - β -methyl-*n*-butaldehyde were converted into their oximes which were reduced to γ -benzylthio-*n*-butylamine and - γ -methyl-*n*-butylamine. The preparation of the acid (I) however made the debenzylation of these amines less important and the pursuit of this part of the project was discontinued.

EXPERIMENTAL.

Acraldehyde (5.6 g.; 6.7 c.c.) was cooled in ice, and thioacetic acid (7.6 g., 7.1 c.c.) was added. A brisk reaction took place and the product, after standing overnight, was distilled under reduced pressure. β -Acetylthiopropaldehyde, b. p. 92–93°/14 mm., n_D^{20} 1.4943, was obtained as a colourless liquid (68%) (Found : C, 45.9; H, 6.4; S, 23.0. $\text{C}_5\text{H}_8\text{O}_2\text{S}$ requires C, 45.4; H, 6.1; S, 24.2%). The *dinitrophenylhydrazones* recrystallised from ethanol in yellow needles, m. p. 127.5° (Found : C, 42.5; H, 4.2. $\text{C}_{11}\text{H}_{10}\text{O}_5\text{N}_2\text{S}$ requires C, 42.3; H, 3.9%). Crotonaldehyde (21 g.) and thioacetic acid (22.5 g.) reacted as above. β -Acetylthio-*n*-butaldehyde had b. p. 91–92°/11 mm., n_D^{20} 1.4882 (65%) (Found : C, 49.8; H, 7.2. $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$ requires C, 49.3; H, 6.9%). The *dinitrophenylhydrazones* crystallised from ethanol in yellow hexagonal plates, m. p. 96° (Found : C, 44.4; H, 4.4. $\text{C}_{11}\text{H}_{10}\text{O}_5\text{N}_2\text{S}$ requires C, 44.2; H, 4.3%).

β -Methylcrotonaldehyde (8 g.) and thioacetic acid (8 g.) similarly gave β -acetylthio- β -methyl-n-butanaldehyde, b. p. 110°/20 mm., n_D^{20} 1.4922 (33%). The *dinitrophenylhydrazones* crystallised from ethanol in yellow rhombic plates, m. p. 94° (Found: C, 45.6; H, 4.6. $C_{13}H_{11}O_4N_4S$ requires C, 45.9; H, 4.7%).

Methylthiol, generated from S-methylisothiouraea sulphate (60 g.) and 5N-sodium hydroxide (100 c.c.) (*Org. Synth.*, Coll. Vol. II, 345), was passed in a slow stream of coal gas into acraldehyde (20 g.) containing triethylamine (2 drops) and cooled to 0°. The mixture was distilled and the fraction, b. p. 165–175°, collected (32 g.; 86%). Redistillation gave β -methylthiopropaldehyde, b. p. 166°/750 mm. (Barger and Coyne, *Biochem. J.*, 1928, 22, 1420, give b. p. 60°/12 mm.), n_D^{20} 1.4824 (Found: C, 46.0; H, 7.5; S, 30.3. Calc. for C_4H_8OS : C, 46.1; H, 7.8; S, 30.8%). The *dinitrophenylhydrazones* crystallised from ethanol in yellowish-orange needles, m. p. 122–123° (Found: C, 42.5; H, 4.4. $C_{10}H_{12}O_4N_4S$ requires C, 42.2; H, 4.3%). Ethylthiol (12 g.) was added dropwise with stirring to a mixture of acraldehyde (10 g.) and triethylamine (5 drops) cooled to 0°. Distillation of the product gave β -ethylthiopropaldehyde, b. p. 180–190° (62%) which, on redistillation, had b. p. 185°/760 mm. (Rothstein, *J.*, 1940, 1560, gives b. p. 60°/10 mm.), n_D^{20} 1.4788 (Found: C, 50.4; H, 8.2; S, 27.4. Calc. for $C_5H_{10}OS$: C, 50.8; H, 8.5; S, 27.1%). The *dinitrophenylhydrazones* crystallised from 90% aqueous ethanol, in orange-red laths, m. p. 100° (Found: C, 44.6; H, 4.6; N, 18.4. $C_{11}H_{14}O_4N_4S$ requires C, 44.3; H, 4.7; N, 18.4%).

To acraldehyde (5.6 g.; 6.7 c.c.) cooled in ice, benzylthiol (12.4 g.) was added, followed by a droplet of piperidine. Heat was evolved. After 15 minutes at 0° and 1 hour at room temperature, ether was added and the solution washed with dilute hydrochloric acid and water, dried, evaporated, and distilled. β -Benzylthiopropaldehyde was obtained as a colourless oil, b. p. 158°/12 mm., n_D^{20} 1.5650 (15 g.; 83%) (Found: C, 66.65; H, 6.90; S, 18.0. $C_{10}H_{12}OS$ requires C, 66.65; H, 6.90; S, 17.8%). The *dinitrophenylhydrazones* crystallised from ethanol in yellow needles, m. p. 112.5° (Found: C, 53.5; H, 4.7. $C_{11}H_{14}O_4N_4S$ requires C, 53.3; H, 4.5%). Crotonaldehyde (28 g.; 32.8 c.c.) and benzylthiol (50 c.c.) were mixed at 0°, a droplet of piperidine was added, and the mixture was kept at room temperature for 3 hours and heated on the steam-bath for 1 hour. The product was isolated as above. β -Benzylthio-n-butanaldehyde (68 g.; 87%) had b. p. 156–157°/10 mm., n_D^{20} 1.5523 (Found: C, 68.2; H, 7.4; S, 16.9. $C_{11}H_{14}OS$ requires C, 68.0; H, 7.3; S, 16.5%). The *dinitrophenylhydrazones* crystallised from ethanol in small yellow leaflets, m. p. 69° (Found: C, 54.2; H, 4.9. $C_{17}H_{18}O_4N_4S$ requires C, 54.5; H, 4.8%).

Benzylthiol (7.5 c.c.) containing piperidine (5 drops) was added to freshly prepared β -methylcrotonaldehyde (5 g.) and the mixture heated on the steam-bath for 3 hours. β -Benzylthioisovaleraldehyde was isolated as above (7 g.; 56%), b. p. 109–110°/0.1 mm., 172°/15 mm., n_D^{20} 1.5484 (Found: C, 69.2; H, 7.6; S, 15.9. $C_{12}H_{16}OS$ requires C, 69.2; H, 7.7; S, 15.4%). The *dinitrophenylhydrazones* crystallised from ethanol in needles, m. p. 113° (Found: C, 55.7; H, 5.1. $C_{18}H_{20}O_4N_4S$ requires C, 55.6; H, 5.2%).

A mixture of β -benzylthiopropaldehyde (1.12 g.) and hydrogen cyanide (1 c.c.) at 0° was treated with a droplet of piperidine. After 0.5 hour at room temperature a small excess of ethereal hydrogen chloride was added and the excess of hydrogen cyanide removed under reduced pressure. After addition of 10% alcoholic ammonia (3 c.c.), the solution was sealed, left overnight, heated at 100° for 0.5 hour, concentrated under reduced pressure, taken up in ether, and filtered. Addition of ethereal hydrogen chloride precipitated an oil which readily crystallised (820 mg.; 55%). Recrystallisation from ethanol-ether gave *α*-amino- γ -benzylthio-n-butyronitrile hydrochloride in rosettes of hair-like needles, m. p. 134–135° (Found: C, 54.45; H, 6.4. $C_{11}H_{12}N_2ClS$ requires C, 54.4; H, 6.2%). β -Benzylthio-n-butanaldehyde (10 g.), hydrogen cyanide (10 c.c.), and potassium cyanide (100 mg.) were mixed. A violent reaction ensued and the mixture was then treated as above with 10% alcoholic ammonia (5 c.c.) and left overnight. *α*-Amino- γ -benzylthio-n-valeronitrile hydrochloride crystallised (9 g.; 68%) and after recrystallisation from ethanol-ether formed slender needles, m. p. 159° (decomp.) (Found: C, 55.7; H, 6.7; N, 11.0; S, 12.5. $C_{12}H_{13}N_2ClS$ requires C, 56.1; H, 6.7; N, 10.9; S, 12.5%). β -Benzylthioisovaleraldehyde (2.9 g.) and hydrogen cyanide (1 c.c.) were treated as above. *α*-Amino- γ -benzylthio- γ -methyl-n-valeronitrile hydrochloride recrystallised from ethanol-ether in triangular plates, m. p. 156–157° (1.0 g.; 27%) (Found: C, 57.4; H, 7.3; N, 9.9. $C_{13}H_{15}N_2ClS$ requires C, 57.6; H, 7.1; N, 10.35%).

β -Benzylthio-n-butanaldehyde (15 g.), potassium acetate (15 g.), hydroxylamine hydrochloride (5.5 g.), and ethanol (100 c.c.) were refluxed for 30 minutes, left over-night, and the oxime precipitated by adding water. A portion of the oily oxime (5 g.) in moist ether (150 c.c.) was reduced by refluxing with amalgamated aluminium (4 g.) overnight. The solution was filtered and the alumina washed with further ether. The filtrate was washed, dried, concentrated, and distilled. The fraction, b. p. 85–95°/0.1 mm., was redistilled to give γ -benzylthio-n-butylamine as a colourless oil (2 g.), b. p. 90–92°/0.1 mm., n_D^{20} 1.5545 (Found: C, 67.3; H, 9.0; N, 7.2. $C_{11}H_{17}NS$ requires C, 67.6; H, 8.8; N, 7.2%). The hydrochloride, prepared with ethereal hydrogen chloride, recrystallised from ethanol-ether in rhombic plates, m. p. 123° (Found: C, 57.1; H, 7.9; N, 6.4. $C_{11}H_{16}NClS$ requires C, 57.0; H, 7.9; N, 6.0%).

β -Benzylthio- β -methyl-n-butanaldehyde (5 g.), potassium acetate (5 g.), hydroxylamine hydrochloride (2 g.), and ethanol (40 c.c.) were treated as before and the product reduced with aluminium amalgam (4 g.). The fraction, b. p. 160–165°/15 mm., was redistilled to give γ -benzylthio- γ -methyl-n-butylamine as a colourless oil (25%), b. p. 102–104°/0.1 mm., n_D^{20} 1.5521 (Found: C, 69.0; H, 8.7; N, 6.1. $C_{13}H_{19}NS$ requires C, 68.8; H, 9.2; N, 6.7). The hydrochloride recrystallised from ethanol-ether, m. p. 157° (Found: C, 58.7; H, 8.0; N, 5.8. $C_{13}H_{18}NClS$ requires C, 58.6; H, 8.2; N, 5.7%).

β -Methylthiopropaldehyde (6.3 g.), anhydrous hydrogen cyanide (5 c.c.), and potassium cyanide (100 mg.) were mixed; a vigorous reaction took place. The excess of hydrogen cyanide was removed under reduced pressure and the residue sealed up with 10% ethanolic ammonia (40 c.c.), heated to 80° for two hours, and left overnight. Ethanol and ammonia were removed under reduced pressure, water and chloroform were added, and the basic fraction was isolated in the chloroform. After removal of the solvent, the residue was taken up in ethanol and ethanolic anhydrous oxalic acid was added. A white solid was precipitated (6.9 g.; 65%). Recrystallisation from ethanol gave *α*-amino- γ -methylthio-n-butyronitrile oxalate in colourless laths, m. p. 200° (decomp.) (Found: C, 41.3; N, 6.5; S, 15.3. $C_8H_{10}N_2S_2O_4$ requires C, 41.1; H, 6.3; N, 16.0%). β -Ethylthiopropaldehyde (10 g.), hydrogen cyanide (10 c.c.), and potassium cyanide (ca. 100 mg.) were treated as above. *α*-Amino- γ -ethylthio-

n-butyronitrile oxalate recrystallised from ethanol in colourless laths, m. p. 230° (decomp.) (3.5 g.) (Found: C, 42.2; H, 7.1; N, 14.5. $C_8H_{12}N_2S_2O_6 \cdot \frac{1}{2}H_2O$ requires C, 42.4; H, 7.1; N, 14.1%).

α -Amino- γ -methylthio-*n*-butyronitrile, from the oxalate (2.5 g.), was refluxed with concentrated hydrochloric acid (10 c.c.) for 1½ hours. The solution was evaporated to dryness under reduced pressure, basified with concentrated aqueous ammonia, and re-evaporated. The residue was dissolved in warm water (20 c.c.), charcoaled, and diluted with ethanol (50 c.c.). Methionine crystallised in glistening plates (1.1 g., 52%), and after recrystallisation from water-ethanol had m. p. 276° (decomp.) (Found: C, 40.3; H, 7.5; N, 9.4. Calc. for $C_6H_{11}O_2NS$: C, 40.3; H, 7.4; N, 9.4%). α -Amino- γ -ethylthio-*n*-butyronitrile oxalate (1 g.) was refluxed with concentrated hydrochloric acid (5 c.c.) for 2 hours and evaporated to dryness under reduced pressure. The residue was basified with concentrated aqueous ammonia, re-evaporated, dissolved in the minimum quantity of boiling water, and left to crystallise. Ethionine crystallised (400 mg., 46%), and recrystallised from water-ethanol in colourless plates, m. p. 265° (decomp.) (Found: C, 44.4; H, 8.1; N, 8.9. Calc. for $C_6H_{13}O_2NS$: C, 44.2; H, 8.0; N, 8.6%).

α -Amino- γ -methylthio-*n*-butyronitrile oxalate (1 g.) was converted into the free base and extracted into chloroform. The solution was concentrated and the residue refluxed in 50% ethanolic carbon disulphide (5 c.c.) for 2 hours. Concentration of the solution and addition of ether left a yellow solid (47%). Recrystallisation from acetone-water gave 5- β -methylthioethylthiohydantoin in sheaves of yellow hair-like needles, m. p. 212° (decomp.) (Found: C, 34.3; H, 4.4; N, 13.8; S, 47.8. $C_8H_{16}N_2S_2$ requires C, 34.9; H, 4.9; N, 13.6; S, 46.5%). The compound was soluble in aqueous sodium hydroxide, but the resulting solution failed to give a coloration with aqueous glyoxal. Repetition of the above reaction in the presence of benzaldehyde (0.5 c.c.) gave 5-benzylideneamino-2-mercapto-4- β -methylthioethylthiazole (95 mg.) which recrystallised from ethanol in yellow needles, m. p. 200° (decomp.) (Found: C, 53.2; H, 5.0; N, 9.8. $C_{15}H_{18}N_2S_2$ requires C, 53.0; H, 4.8; N, 9.5%). It gave a red coloration on warming with alkali and glyoxal. α -Amino- γ -ethylthio-*n*-butyronitrile, from the oxalate (1 g.), was refluxed with 50% ethanolic carbon disulphide (5 c.c.) and treated as above. 5- β -Ethylthioethylthiohydantoin (40%) recrystallised from ethanol in fine yellow hairs, m. p. 196–197° (decomp.) (Found: C, 37.2; H, 5.2; N, 12.4. $C_7H_{12}N_2S_2$ requires C, 38.2; H, 5.5; N, 12.7%).

5- β -Methylthioethylthiohydantoin (430 mg.) was refluxed with a 1:1 mixture of acetic and concentrated hydrochloric acids (10 c.c.) for two hours and the solution was concentrated under reduced pressure. The solution was made alkaline with ammonia and again evaporated under reduced pressure, taken up in water (5 c.c.), filtered, and diluted with ethanol (15 c.c.). Methionine separated in glistening plates, m. p. 270° (decomp.) (75 mg., 25%), on standing overnight. A similar hydrolysis of 5-benzylideneamino-2-mercapto-4- β -methylthioethylthiazole (190 mg.) gave methionine in plates, m. p. 271° (decomp.) (25 mg., 25%).

α -Amino- γ -benzylthio-*n*-butyronitrile hydrochloride (860 mg.) and 47% aqueous hydrobromic acid (17.5 c.c.) were heated to 100° for 3½ hours with frequent shaking, and the solution evaporated under reduced pressure. The residue was taken up in water, charcoaled, and neutralised with 2*N*-ammonia. A flocculent precipitate of S-benzylhomocysteine (α -amino- γ -benzylthio-*n*-butyric acid) was obtained (450 mg.; 60%), m. p. 190–191°. The m. p. was undepressed on admixture with authentic material. α -Amino- γ -benzylthio-*n*-valeronitrile hydrochloride (257 mg.) and concentrated hydrochloric acid (3 c.c.) were heated in a sealed tube at 100° for 16 hours. The product was worked up as above. α -Amino- γ -benzylthio-*n*-valeric acid (110 mg.) recrystallised from 50% methanol in small plates, m. p. 215–216° (decomp.) (Found: C, 60.0; H, 7.4; N, 5.5. $C_{12}H_{17}O_2NS$ requires C, 60.2; H, 7.15; N, 5.9%). α -Amino- γ -benzylthio- γ -methyl-*n*-valeronitrile hydrochloride (3.8 g.) was added to aqueous sodium hydrogen carbonate, the free base was extracted into ether, the extract was dried and then concentrated under reduced pressure, and the residual oil was refluxed with 50% ethanol-carbon disulphide (20 c.c.) for 3 hours. After concentration under reduced pressure, the solid was filtered off and washed with a little cold ethanol. Further product was obtained by treating the mother liquors with ether (3.1 g.; 70%). 5-Amino-2-mercapto-4- β -benzylthioisobutylthiazole recrystallised from ethanol-water in pale yellow rhombic plates, m. p. 237° (Found: C, 53.9; H, 5.5; N, 9.2; S, 30.6. $C_{14}H_{19}N_2S_2$ requires C, 54.2; H, 5.8; N, 9.0; S, 31.0%). Addition of 50% aqueous glyoxal to a solution of the thiazole in 2*N*-sodium hydroxide gave a red coloration, and after acidification, the bisazomethine derivative was precipitated; it recrystallised from pyridine-water in fine red hairs, m. p. 238° [Found: C, 56.3; H, 5.6; N, 9.0. ($C_{18}H_{21}N_2S_2$) requires C, 56.1; H, 5.4; N, 8.7%]. The thiazole (5 g.) was refluxed in 50% acetic acid-concentrated hydrochloric acid (40 c.c.) for 2 hours, the solution concentrated under reduced pressure, and the residue taken up in water, filtered, and neutralised with 2*N*-ammonia. α -Amino- γ -benzylthio- γ -methyl-*n*-valeric acid separated as a flocculent buff precipitate which recrystallised from hot water in colourless plates, m. p. 178° (2.4 g.; 59%) (Found: C, 61.2; H, 7.4; N, 5.6. $C_{13}H_{19}O_2NS$ requires C, 61.6; H, 7.6; N, 5.5%). The product gave a strong ninhydrin reaction.

The preceding S-benzyl compound (2.4 g.) in liquid ammonia (40 c.c.) was stirred and reduced with sodium (*ca.* 0.6 g.) added in small pieces until a permanent blue colour was obtained. Ammonium chloride (2 g.) was added and the solution evaporated to dryness and evacuated on a water pump to remove remaining traces of ammonia. Etheral hydrogen chloride was added, the solution was filtered, and the residue thoroughly extracted with ethanol. The extract was concentrated under reduced pressure, the residue extracted with chloroform, and the extract re-concentrated. The residual oil solidified under dry ether (1.4 g.; 73%). Recrystallisation from ethanol-ether gave micro-prisms of α -amino- γ -mercapto- γ -methyl-*n*-valeric acid, m. p. 219° (decomp.) (Found: C, 39.4; H, 6.8; N, 7.3; Cl, 18.4; S, 16.6. $C_6H_{14}O_2NCIS$ requires C, 36.07; H, 7.0; N, 7.0; Cl, 17.8; S, 16.0%). The product gave a strong transient purple colour with alkaline nitroprusside, a weak red-brown ferric chloride colour after addition of aqueous sodium hydrogen carbonate, and a deep red-brown coloration with ninhydrin reagent.

α -Amino- γ -benzylthio- γ -methyl-*n*-valeronitrile (1 g.) was refluxed with 50% acetic acid-concentrated hydrochloric acid (10 c.c.) for 2 hours. The solution was concentrated under reduced pressure, and the residue dissolved in water, filtered, and neutralised with 2*N*-ammonia. The crystalline solid which separated was α -amino- γ -benzylthio- γ -methyl-*n*-valeric acid, m. p. 175° (110 mg. or 12%).

α -Amino- γ -mercapto- γ -methyl- n -valeric acid as its hydrochloride (250 mg.), benzaldehyde (1 c.c.), and methanolic hydrogen chloride (2 c.c.) were heated on the steam-bath for 15 minutes; cooled, and the product was extracted with ether. The residual solid was dissolved in water and the solution neutralised with 2N-ammonia. The oil which separated crystallised on scratching and was recrystallised from aqueous ethanol to give needles of 4-carbomethoxy-2-phenyl-6:6-dimethylthiazan, m. p. 105° (Found: C, 63.4; H, 7.2; N, 5.3. $C_{14}H_{18}O_2NS$ requires C, 63.35; H, 7.2; N, 5.3%).

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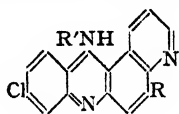
[Received, January 23rd, 1947.]

321. Synthetic Antimalarials. Part XXII. Some Quinolylamino-substituted Pyrimidine Derivatives.

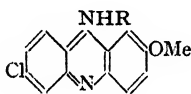
By F. H. S. CURD, W. GRAHAM, (MISS) D. N. RICHARDSON, and F. L. ROSE.

By adapting the methods of preparation utilised for the corresponding anilino-compounds (see earlier papers in this series), series of 2-quinolylamino-4-dialkylaminoalkylamino- and 4-quinolylamino-2-dialkylaminoalkylamino-6-methylpyrimidines have been prepared. Whereas some of the former show activity against *P. gallinaceum* in chicks, the latter are all devoid of activity. Possible explanations for these observations are discussed.

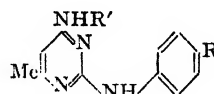
THE preparation of derivatives of 8-chloro-3:4:2':3'-pyridoacridine (I; R = H, R' = dialkylaminoalkyl), possessing considerable antimalarial activity against *P. gallinaceum* in chicks, has recently been reported by Dobson and Kermack (*J.*, 1946, 150). Such compounds may be considered as related to the mepacrine type of antimalarial (II), the 3-methoxy-group of the latter being replaced by the heterocyclic atom of the pyrido-ring. Reference to the structure (III) of the active 2-*p*-substituted anilino-4-dialkylaminoalkylamino-6-methylpyrimidines, described in Parts I and II (*J.*, 1946, 343, 351) showed that a related modification was possible with respect to the substituent R giving rise to quinoline derivatives of type (IV). Further incentive to the preparation of such compounds was provided by the known activity of (III; R = NMe₂, R' = [CH₂]₃·NEt₂) which suggested that activity might be encountered if the dimethylamino-group was replaced by the basic nitrogen atom of a fused heterocyclic ring.



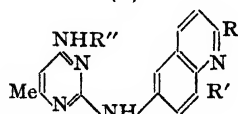
(I.)



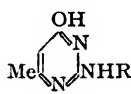
(II.)



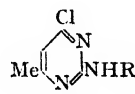
(III.)



(IV.)



(V.)



(VI.)

6-Aminoquinoline was therefore condensed with 4-hydroxy-2-methylthio-6-methylpyrimidine in boiling 2-ethoxyethanol solution to give 2-(6'-quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 6-quinolyl), which was converted smoothly into 4-chloro-2-(6'-quinolylamino)-6-methylpyrimidine (VI; R = 6-quinolyl) by treatment with phosphoryl chloride. Condensation of this chloropyrimidine with β -diethylaminoethylamine, γ -diethylaminopropylamine, γ -dimethylaminopropylamine, δ -diethylaminobutylamine and δ -diethylamino- α -methylbutylamine then gave a series of 2-(6'-quinolylamino)-4-dialkylaminoalkylamino-6-methylpyrimidines (IV; R = R' = H, R'' = [CH₂]₃·NEt₂, [CH₂]₃·NEt₂, [CH₂]₃·NMe₂, [CH₂]₄·NEt₂, and CHMe·[CH₂]₃·NEt₂).

By a similar series of reactions using 6-aminoquinaldine in place of 6-aminoquinoline in the initial condensation with 4-hydroxy-2-methylthio-6-methylpyrimidine there were prepared, by way of (V; R = 6-quinaldyl) and (VI; R = 6-quinaldyl), 2-(6'-quinaldylamino)-4- β -diethylaminoethylamino-6-methylpyrimidine (IV; R = Me, R' = H, R'' = [CH₂]₃·NEt₂) and the corresponding 4- γ -diethylaminopropylamino-derivative (IV; R = Me, R' = H, R'' = [CH₂]₃·NEt₂).

All the above compounds showed some antimalarial activity when tested against *P. gallinaceum* in chicks (see table of activities) and it therefore became necessary to investigate the

to prepare the analogous quinoline compound, 2-(5'-bromo-8'-quinolylamino)-4- β -diethylamino-ethylamino-6-methylpyrimidine (VIII; R = H, R' = Br) was unsuccessful. It was found that

the bromine atom in 5-bromo-8-aminoquinoline was somewhat labile, and when the bromo-compound was heated with 4-hydroxy-2-methylthio-6-methylpyrimidine in 2-ethoxy-ethanol at 140°, hydrobromic acid, resulting from its decomposition, brought about hydrolysis of the pyrimidine intermediate to 4-methyluracil.

This investigation has also been concerned with the preparation of 2-dialkylaminoalkylamino-4-(quinolylamino)-6-methylpyrimidines of types (XII) and (XIII) in which the quinolylamino-substituent and the dialkylaminoalkylamino-side chain have been interchanged. 4-Chloro-2- β -diethylaminoethylamino-6-methylpyrimidine (VI; $R = [CH_2]_2 \cdot NEt_2$) (Curd *et al.*, *J.*, 1946, 373) was condensed with 6-aminoquinoline by heating it at 140° to give 4-(6'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XII; $R = H$) and with 8-aminoquinoline to give 4-(8'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XIII; $R = H$). Reactions of this type were also effected by boiling in dilute hydrochloric acid. In this way 6-amino-8-methoxyquinoline gave 4-(8'-methoxy-6'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XII; $R = OMe$) and 5-bromo-8-aminoquinoline afforded 4-(5'-bromo-8'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XIII; $R = Br$).

These compounds, like those of the previous series, were without antimalarial activity against *P. gallinaceum* in chicks. The contrast between the inactivity of 4-(6'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XII; $R = H$) and the activity of the isomeric 2-(6'-quinolylamino)-4- β -diethylaminoethylamino-6-methylpyrimidine (IV; $R = R' = H$, $R'' = [CH_2]_2 \cdot NEt_2$), finds an analogy in the corresponding naphthylamino-derivatives. Thus 4-(6'-bromo- β -naphthylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine and related compounds show little or no activity (Part VI, *J.*, 1946, 370), whereas the isomeric 2-(6'-bromo- β -naphthylamino)-4- β -diethylaminoethylamino-6-methylpyrimidine is highly active (Curd *et al.*, *J.*, 1946, 366).

TABLE I.

Antimalarial Activities.

The antimalarial tests were carried out, as in previous investigations of this series, by our colleague Dr. D. G. Davey using *P. gallinaceum* in chicks (cf. Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, 39, 139; Davey, *ibid.*, 1946, 40, 52). The results are expressed in the same way as in previous papers of this series.

(a) 2-(6'-Quinolylamino)- and 2-(6'-Quinaldylamino)-4-dialkylaminoalkylamino-6-methylpyrimidines.

Ref. No.	Substituent at		Dose mg./kg.	Activity.
	2-position.	4-position.		
3749	Quinolyl	$NH \cdot [CH_2]_2 \cdot NEt_2$	120	++
			80	+
3707	Quinolyl	$NH \cdot [CH_2]_3 \cdot NEt_2$	160	+
			80	+
			40	--
3835	Quinolyl	$NH \cdot [CH_2]_3 \cdot NMe_2$	160	+
			80	+
3878	Quinolyl	$NH \cdot [CH_2]_4 \cdot NEt_2$	120	+
3864	Quinolyl	$NH \cdot CHMe \cdot [CH_2]_3 \cdot NEt_2$	120	±
			80	--
3750	Quinaldyl	$NH \cdot [CH_2]_2 \cdot NEt_2$	80	+
			40	--
3692	Quinaldyl	$NH \cdot [CH_2]_3 \cdot NEt_2$	120	++
			80	+

(b) 2-(Quinolylamino)-4- β -diethylaminoethylamino-6-methylpyrimidines.

Ref. No.	Substituent at 2.	Dose, mg./kg.	Activity.
5186	5'-Quinolyl	80	--
5187	8'-Quinolyl	80	--
5188	6'-Methoxy-8'-quinolyl	320	--
		240	--
5719	8'-Methoxy-6'-quinolyl	160	--

(c) 4-(Quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidines.

Ref. No.	Substituent at 4.	Dose, mg./kg.	Activity.
5398	6'-Quinolyl	160	--
5399	8'-Quinolyl	160	--
5720	8'-Methoxy-6'-quinolyl	160	--
5721	5'-Bromo-8'-quinolyl	160	--

Some of the compounds were also tested for prophylactic action against *P. gallinaceum* in chicks by the method described by Davey (*Ann. Trop. Med. Parasit.*, 1946, 40, 453); 5719, 5720, 5721, and 5398 at 160 mg./kg., 5188 at 240 mg./kg., and 5187 at 80 mg./kg., but all proved to be inactive.

The following points may be noted in connection with the preparation of the requisite quinoline intermediates. 5- and 8-Nitroquinolines, prepared from quinoline in 85% total yield by a method using fuming nitric acid and 20% oleum in place of the 40% oleum used by Meigen (*J. pr. Chem.*, 1908, 77, 472) and 65% oleum by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1940, 62, 1643), were reduced to the corresponding aminoquinolines with iron dust in dilute acetic acid (Dikshoorn, *Rec. Trav. chim.*, 1929, 48, 153). 6-Nitro-8-methoxyquinoline was prepared by a modified Skraup reaction (cf. E.P. 394,416) using arsenic acid as oxidising agent. When sodium *m*-nitrobenzenesulphonate was used as oxidising agent the only product obtained was a yellow crystalline substance, presumed to be the 4-nitro-2-methoxyanil of β -4'-nitro-2'-methoxyanilinopropaldehyde (Xa), or the cyclic analogue 4-(4'-nitro-2'-methoxyanilino)-6-nitro-8-methoxy-1:2:3:4-tetrahydroquinoline (Xb), probable intermediates in the Skraup synthesis. Reduction of 6-nitro- to 6-amino-8-methoxyquinoline by means of stannous chloride (Fourneau *et al.*, *Ann. Inst. Pasteur*, 1930, 44, 748) was not very satisfactory, and so attempts were made to increase the yield by reduction with iron dust and dilute acetic acid, iron dust and hydrochloric acid, or Raney nickel and hydrogen at 80 atmospheres and at 30 atmospheres. The best yield (50%) was obtained using the last named conditions.

EXPERIMENTAL.

2-(6'-Quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 6-quinolyl).—4-Hydroxy-2-methylthio-6-methylpyrimidine (33.2 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, 29, 478), 6-aminoquinoline (72 g.), and 2-ethoxyethanol (75 c.c.) were refluxed for 48 hours with stirring. Methylthiol was evolved. After cooling, the product was filtered off, washed well with hot alcohol, and dried (yield, 35 g.), m. p. 256—258°. The m. p. was unchanged by crystallisation from butanol from which the substance separated as colourless thick prisms (Found: C, 66.6; H, 4.7. $C_{14}H_{12}ON_4$ requires C, 66.7; H, 4.8%).

2-(6'-Quinaldylamino)-4-hydroxy-6-methylpyrimidine (V; R = 6-quinaldyl).—Prepared in an exactly similar manner using 6-aminoquinaldine in place of 6-aminoquinoline, the compound separated from 2-ethoxyethanol in clusters of small colourless needles, m. p. 284° (Found: C, 67.4; H, 5.3; N, 20.4. $C_{15}H_{14}ON_4$ requires C, 67.7; H, 5.3; N, 21.05%).

4-Chloro-2-(6'-quinolylamino)-6-methylpyrimidine (VI; R = 6-quinolyl).—The corresponding hydroxy-compound (28 g.) and phosphoryl chloride (95 c.c.) were refluxed for 4 hours. The excess of phosphoryl chloride was then removed under reduced pressure and the residue treated with a small amount of crushed ice. The solid product was filtered off, dissolved in hot water (150 c.c.) with hydrochloric acid (12.5 c.c.), and the resulting solution treated with decolorising carbon and filtered. The filtrate was cooled and hydrochloric acid (22.5 c.c.) added. The precipitated hydrochloride was filtered off, drained well, and dissolved in warm water (250 c.c.). Gradual addition of ammonia to the cooled solution precipitated the base, which was filtered off, dried in a vacuum, and crystallised from alcohol. It formed colourless prisms, m. p. 183—185° (Found: N, 20.5; Cl, 12.7. $C_{14}H_{11}N_4Cl$ requires N, 20.7; Cl, 13.1%).

4-Chloro-2-(6'-quinaldylamino)-6-methylpyrimidine (VI; R = 6-quinaldyl), prepared in an analogous manner from 2-(6'-quinaldylamino)-4-hydroxy-6-methylpyrimidine (33.25 g.) and phosphoryl chloride (85 c.c.), crystallised from 2-ethoxyethanol in colourless prisms, m. p. 235° (Found: N, 19.9; Cl, 12.5. $C_{15}H_{13}N_4Cl$ requires N, 19.85; Cl, 12.5%).

5- and 8-Nitroquinoline. —The method employed was essentially that of Fieser and Hershberg (*loc. cit.*). Quinoline sulphate, from quinoline (77.5 g.) and concentrated sulphuric acid (35 c.c.), dissolved in 20% oleum (210 g.), was nitrated with nitric acid (d 1.5; 105 g.) giving 5-nitroquinoline (42 g.) and 8-nitroquinoline (45 g.).

6-Nitro-8-methoxyquinoline. —A mixture of 2-amino-5-nitroanisole (100 g.), sulphuric acid (1000 g. of 70%), glycerol (200 g.), and arsenic acid (333 g. of 80%) was heated to boiling during $\frac{1}{2}$ hour and then refluxed for 4 hours with stirring. The temperature of the boiling mixture dropped from 138° to 133° during the course of the reaction. After cooling, the reaction mixture was drowned into water (3 l.), and the solution stirred with decolorising carbon and filtered. Addition of sodium hydroxide solution to the filtrate precipitated 6-nitro-8-methoxyquinoline which was filtered off, washed with water, and crystallised from alcohol, m. p. 149—150° (yield, 82.5 g.). By recrystallisation from acetone the m. p. was raised to 152—153°. Fourneau *et al.* (*loc. cit.*) give m. p. 149°. In an experiment using sodium *m*-nitrobenzenesulphonate as oxidising agent the only material isolated was a substance crystallising from alcohol in yellow needles, m. p. 126—127°. This was presumed to be (Xa) or (Xb) (Found: C, 54.5; H, 4.2; N, 15.0. $C_{17}H_{13}O_2N_4$ requires C, 54.5; H, 4.8; N, 15.0%).

6-Amino-8-methoxyquinoline. —6-Nitro-8-methoxyquinoline (12 g.) dissolved in alcohol (600 c.c.) was hydrogenated in presence of Raney nickel (8 c.c. of sludge) in the cold at 30 atmospheres. After removal of the catalyst and on slight concentration of the alcohol solution a yellow solid separated which crystallised from alcohol-chloroform in yellow needles, m. p. ca. 350° (Found: C, 68.7; H, 4.3; N, 16.5%). Evaporation of the alcohol solution to dryness gave a dark red gummy solid from which, after several crystallisations from ethyl acetate, there was obtained 6-amino-8-methoxyquinoline (yield, 4.6 g.) as yellow laminae, m. p. 167—169°. Fourneau *et al.* (*loc. cit.*) give m. p. 168°.

2-(8'-Quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 8-quinolyl). —8-Aminoquinoline (34 g.), 4-hydroxy-2-methylthio-6-methylpyrimidine (34 g.), and 2-ethoxyethanol (40 c.c.) were heated together in an oil-bath at 135—145° for 70 hours. The mixture was then extracted several times with boiling alcohol leaving undissolved 2-(8'-quinolylamino)-4-hydroxy-6-methylpyrimidine (yield, 32.8 g.), m. p. 263—265°, unchanged after recrystallisation from 2-ethoxyethanol from which it separated in colourless prisms (Found: C, 66.5; H, 4.8. $C_{14}H_{12}ON_4$ requires C, 66.7; H, 4.8%).

2-(5'-Quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 5-quinolyl).—Prepared in the same way from 5-aminoquinoline (10 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (10 g.) in 2-ethoxyethanol (11.4 c.c.), this substance formed a fine white powder (yield, 8.1 g.), m. p. 286—290°, which could not be crystallised.

2-(6'-Methoxy-8'-quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 6-methoxy-8-quinolyl), similarly obtained from 8-amino-6-methoxyquinoline (19 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (15 g.) in 2-ethoxyethanol (25 c.c.), on crystallisation from 2-ethoxyethanol formed colourless needles (yield, 12.6 g.), m. p. 245—246° (Found: C, 64.2, 64.2; H, 4.5, 4.7. $C_{15}H_{14}O_4N_4$ requires C, 63.85; H, 5.0%).

2-(8'-Methoxy-6'-quinolylamino)-4-hydroxy-6-methylpyrimidine (V; R = 8-methoxy-6-quinolyl) was obtained in the same manner from 6-amino-8-methoxyquinoline (7.9 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (6.8 g.) by reaction in 2-ethoxyethanol (9 c.c.). It formed a tan-coloured microcrystalline powder (yield, 5 g.), m. p. 231—235°, from alcohol (Found: C, 62.7; H, 4.7; N, 18.2. $C_{15}H_{14}O_4N_4$, 0.5 C_6H_5 ·OH requires C, 62.95; H, 5.6; N, 18.35%).

4-Chloro-2-(8'-quinolylamino)-6-methylpyrimidine (VI; R = 8-quinolyl).—2-(8'-Quinolylamino)-4-hydroxy-6-methylpyrimidine (5 g.) and freshly distilled phosphoryl chloride (25 c.c.) were heated by means of an oil-bath for 4 hours at 125°. Excess of phosphoryl chloride was removed under diminished pressure and the residue treated with ice and dissolved in hydrochloric acid. The acid solution was filtered, carefully neutralised with ammonia, and the product filtered off, washed with water, and dried in a vacuum. It was then extracted thrice with boiling alcohol (200 c.c.) and filtered from insoluble material (1.5 g.). Concentration of the alcohol solution gave the chloropyrimidine which after recrystallisation from alcohol formed colourless prisms (yield, 3.4 g.), m. p. 146—148° (Found: C, 62.2; H, 4.3. $C_{14}H_{11}N_4Cl$ requires C, 62.1; H, 4.1%).

4-Chloro-2-(5'-quinolylamino)-6-methylpyrimidine (VI; R = 5-quinolyl).—The corresponding hydroxypyrimidine (11.5 g.) and freshly distilled phosphoryl chloride (45 c.c.) were heated at 120° in an oil-bath for 4 hours. After removal of the excess of phosphoryl chloride under reduced pressure at 100° the residue was treated with ice and dissolved in hydrochloric acid. After filtration, the solution was rendered alkaline with ammonia and the precipitated product filtered off, washed with water and dried in a vacuum. It crystallised from alcohol as colourless prisms (yield, 9.6 g.), m. p. 198—200° (Found: C, 62.5; H, 4.2. $C_{14}H_{11}N_4Cl$ requires C, 62.1; H, 4.1%).

4-Chloro-2-(6'-methoxy-8'-quinolylamino)-6-methylpyrimidine (VI; R = 6-methoxy-8-quinolyl), similarly obtained from 2-(6'-methoxy-8'-quinolylamino)-4-hydroxy-6-methylpyrimidine (9.7 g.) and phosphoryl chloride (39 c.c.), formed pale yellow prisms from alcohol (yield, 8.7 g.), m. p. 139—141° (Found: C, 59.7; H, 4.2. $C_{15}H_{13}ON_4Cl$ requires C, 59.9; H, 4.3%).

4-Chloro-2-(8'-methoxy-6'-quinolylamino)-6-methylpyrimidine (VI; R = 8-methoxy-6-quinolyl), prepared in the same way from the appropriate hydroxypyrimidine (5.2 g.) and phosphoryl chloride (21 c.c.), crystallised from benzene as pale yellow prismatic needles (yield, 5 g.), m. p. 213—215° (Found: C, 59.6; H, 4.1; N, 18.7. $C_{15}H_{13}ON_4Cl$ requires C, 59.9; H, 4.3; N, 18.6%).

Preparation of 2-Quinolylamino-4-dialkylaminoalkylamino-6-methylpyrimidines.—The 4-chloro-2-quinolylamino-6-methylpyrimidine (0.25 g.-mol.) and dialkylaminoalkylamine (0.25 × 1.15—2 g.-mol.) were heated at 125—135° (oil-bath) for 8 hours with stirring. After cooling, the resulting melt was dissolved in warm dilute hydrochloric acid, and the cooled solution basified with sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water and shaken out several times with 5% acetic acid. The combined acid extracts were made alkaline with sodium hydroxide and the liberated base was taken into chloroform. After drying (K_2CO_3) and evaporation of the chloroform an oily base remained. This usually solidified on standing, or on trituration with warm light petroleum (b. p. 60—80°) and was then crystallised from light petroleum (b. p. 100—120°). Where the base could not be crystallised, it was converted into the dihydrochloride by dissolving it in 2N-hydrochloric acid and evaporation under reduced pressure at as low temperature as possible. The residue was dried and freed from adhering acid by repeated evaporation to dryness with alcohol-benzene and then purified by crystallisation. Table II details and gives a description of the compounds prepared.

5-Bromo-8-aminoquinoline.—8-Aminoquinoline was converted into its acetyl derivative and brominated in acetic acid. Contrary to the report of Claus and Setzer (*J. pr. Chem.*, 1896, 53, 404) it was found that the hydrobromide of 5-bromo-8-acetamidoquinoline was dissociated in water. The acetyl derivative was hydrolysed to 5-bromo-8-aminoquinoline, the hydrochloride of which was likewise dissociated in water. After two crystallisations from alcohol, 5-bromo-8-aminoquinoline formed fine yellow needles, m. p. 109—110° (Found: C, 48.4; H, 3.5. Calc. for $C_9H_7N_2Br$: C, 48.4; H, 3.15%). Claus and Setzer (*loc. cit.*) give m. p. 104°.

Attempted Condensation of 5-Bromo-8-aminoquinoline and 4-Hydroxy-2-methylthio-6-methylpyrimidine.—The pyrimidine (9.6 g.), 5-bromo-8-aminoquinoline (15 g.), and 2-ethoxyethanol (11 c.c.) were heated in an oil-bath at 135—145° for 72 hours. From the dark red mixture the only products isolated were: (a) 4-methyluracil (5 g.), m. p. 312° (efferv.), identified by conversion into 5-bromo-4-methyluracil, m. p. 230° (Behrend, *Annalen*, 1885, 229, 8), and (b) a water-soluble dark red gum (13 g.) which gave a positive test for ionised bromine. Ionised bromine was detected after 5-bromo-8-aminoquinoline had been heated with 2-ethoxyethanol at 140° for 8 hours, but the bromine in the acetyl derivative showed no such lability when heated with β -diethylaminoethylamine at this temperature.

4-(8'-Quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (XIII; R = H).—4-Chloro-2- β -diethylaminoethylamino-6-methylpyrimidine (7.2 g.) (Curd *et al.*, *J.*, 1946, 373) and 8-aminoquinoline (5.4 g. 1.25 mol.) were heated in an oil-bath for 8 hours at 140°. The mixture was dissolved in dilute hydrochloric acid, the solution basified with sodium hydroxide, and extracted with chloroform. The chloroform extract was washed with water and then extracted several times with 5% acetic acid. The total acid extract was made alkaline with sodium hydroxide and the precipitated oil extracted with chloroform. The extract, after being washed and dried, was evaporated to dryness, giving the base as a red oil (7 g.) which could not be crystallised. This was dissolved in dilute hydrochloric acid and the solution evaporated to dryness under reduced pressure followed by repeated evaporation with alcohol—

TABLE II.
2-Quinolylamino-4-dialkylaminoalkylamino-6-methylpyrimidines.

Substituents,		Derivative.	M. p.	Formula.	Analysis.					
at position 2.	at position 4.				Found (%).			Required (%).		
6-Quinolyl	NH·[CH ₂] ₃ ·NEt ₂	—	124–126° (a)	C ₂₀ H ₂₄ N ₆	C.	H.	N.	C.	H.	N.
"	NH·[CH ₂] ₃ ·NEt ₂	—	86–90 (b)	C ₂₁ H ₂₄ N ₆ ·0.5H ₂ O	68.0	7.0	23.8	68.6	7.4	24.0
"	NH·[CH ₂] ₃ ·NMe ₂	—	153 (a) (c)	C ₁₉ H ₂₂ N ₆	67.4	7.8	22.6	67.6	7.8	22.6
"	NH·[CH ₂] ₃ ·NEt ₂	—	119–120 (d)	C ₁₉ H ₂₂ N ₆	67.6	7.2	24.3	67.85	7.1	25.0
"	NH·CHMe·[CH ₂] ₃ ·NEt ₂	—	120–122 (a)	C ₂₀ H ₂₄ N ₆	69.6	7.9	22.2	69.8	7.9	22.2
6-Quinaldyl	NH·CHMe·[CH ₂] ₃ ·NEt ₂	—	132–133 (a)	C ₂₁ H ₂₄ N ₆	70.1	8.0	21.5	70.4	8.2	21.4
"	NH·[CH ₂] ₃ ·NEt ₂	—	130–131 (a)	C ₂₁ H ₂₄ N ₆	69.1	7.5	22.5	69.2	7.7	23.1
5-Quinolyl	NH·[CH ₂] ₃ ·NEt ₂	—	110–111 (d)	C ₂₀ H ₂₄ N ₆	69.7	7.9	21.6	69.8	7.9	22.2
	NH·[CH ₂] ₃ ·NEt ₂	—			68.6	7.4	23.9	68.6	7.4	24.0
8-Quinolyl	—	Trihydrochloride	258–260 (e)	C ₂₀ H ₂₄ N ₆ ·3HCl·2.5H ₂ O	47.7	6.15	21.1	47.6	6.7	21.1
	"	Dihydrochloride	267–270 (d)	C ₂₀ H ₂₄ N ₆ ·2HCl·1.5H ₂ O	53.6	6.7	16.1	53.4	6.9	15.6
	"	"	(f)		53.7	6.8				
6-Methoxy-8-quinolyl	"	"	262–264 (g)	C ₂₁ H ₂₆ ON ₆ ·2HCl·2.5H ₂ O	50.6	6.7	14.6	50.6	7.0	14.3
8-Methoxy-6-quinolyl	"	"	260–262 (h)	C ₂₁ H ₂₆ ON ₆ ·2HCl·3.5H ₂ O	48.4	7.3		48.8	7.2	

(a) Colourless laminae.

(b) Purified by preliminary vacuum distillation before crystallisation.

(c) Crystallised first from dilute alcohol.

(d) Colourless prisms.

(e) Crystallised from alcohol-ether; yellow needles.

(f) Crystallised from ether-alcohol.

(g) Crystallised from alcohol; colourless fine needles.

(h) Crystallised from alcohol-ether; slightly hygroscopic fine yellow needles, m. p. 202° (efferv.) solidifying and remelting at 260–262°. After drying for 2 hours in a vacuum at 100° it was deeper yellow in colour and had only one m. p. 260° (Found: N, 17.0; Cl, 14.2. C₂₁H₂₆ON₆·2HCl·2.5H₂O requires N, 16.9; Cl, 14.3%).

benzene. The remaining *dihydrochloride* crystallised from alcohol as colourless needles, m. p. 249–251° (Found: C, 54.0, 54.2; H, 6.9, 6.9; N, 19.5, 19.4. $C_{20}H_{22}N_4 \cdot 2HCl \cdot H_2O$ requires C, 54.4; H, 6.8; N, 19.1%).

4-(6'-*Quinolylamino*)-2- β -diethylaminoethylamino-6-methylpyrimidine (XII; R = H), obtained in a similar manner from 4-chloro-2- β -diethylaminoethylamino-6-methylpyrimidine and 6-aminoquinoline, crystallised from benzene-cyclohexane in pale tan-coloured prisms, m. p. 160° (Found: C, 68.8, 68.7; H, 7.3, 7.5; N, 23.8. $C_{20}H_{28}N_6$ requires C, 68.6; H, 7.4; N, 24.0%). The corresponding *trihydrochloride* crystallised from alcohol, forming yellow needles, m. p. 258–261° (Found: C, 47.2; H, 6.8; N, 16.6. $C_{20}H_{28}N_6 \cdot 3HCl \cdot 2.5H_2O$ requires C, 47.6; H, 6.7; N, 16.65%).

4-(8'-*Methoxy-6'-quinolylamino*)-2- β -diethylaminoethylamino-6-methylpyrimidine (XII; R = OMe).—4-Chloro-2- β -diethylaminoethylamino-6-methylpyrimidine (2.8 g., 1 mol.), 6-amino-8-methoxyquinoline (2 g., 1 mol.), concentrated hydrochloric acid (1.27 c.c., 1.1 mol.), and water (12.7 c.c.) were refluxed for 2 hours. The clear solution, when cold, was made alkaline with sodium hydroxide and worked up as described above for this type of compound, giving 4-(8'-methoxy-6'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine (yield, 3.7 g.) which formed pale yellow needles from aqueous methanol, m. p. 201–203° (Found: C, 66.3; H, 7.2; N, 22.2. $C_{21}H_{28}ON_6$ requires C, 66.3; H, 7.3; N, 22.1%). The *trihydrochloride*, prepared in the usual manner, crystallised from alcohol in slightly yellow hygroscopic needles, m. p. 222–224° (Found: C, 47.4; H, 6.7. $C_{21}H_{28}ON_6 \cdot 3HCl \cdot 2.5H_2O$ requires C, 47.15; H, 6.7%).

4-(5'-*Bromo-8'-quinolylamino*)-2- β -diethylaminoethylamino-6-methylpyrimidine (XIII; R = Br).—4-Chloro-2- β -diethylaminoethylamino-6-methylpyrimidine (2.9 g.), 5-bromo-8-aminoquinoline (2.67 g.), 10N-hydrochloric acid (1.32 c.c.), and water (13.2 c.c.) were boiled. Initially the mixed solids melted, and as the oil dissolved a solid began to separate. The mixture was refluxed for 2 hours and then left overnight. The 4-(5'-bromo-8'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine *dihydrochloride* which separated was collected, dried, and crystallised from alcohol-ethyl acetate forming colourless needles (yield, 4.6 g.), m. p. 268–270° (Found: C, 47.6; H, 5.3; N, 16.5; Cl, 13.0. $C_{20}H_{25}N_4Br \cdot 2HCl$ requires C, 47.8; H, 5.4; N, 16.6; Cl, 14.1%). The free base was obtained by working up the hydrochloric acid mother liquor in the usual manner and also by treatment of the *dihydrochloride* with sodium hydroxide. It crystallised from light petroleum (b. p. 80–100°) as pale yellow rhombs, m. p. 133–134° (Found: C, 55.6; H, 5.7. $C_{20}H_{25}N_4Br$ requires C, 55.9; H, 5.8%).

This research was carried out under a wartime collaborative agreement between the Medical Research Council and Imperial Chemical Industries Ltd. The authors desire to express their thanks to Professor J. W. Cook, F.R.S., and Dr. T. S. Stevens for their interest in the work. One of us (W. G.) gratefully acknowledges the receipt of a grant from the Medical Research Council.

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[Received, January 27th, 1947.]

322. Reactions of Benzthiazole Derivatives. Part V. Observations on the Formation of 2-Acetonylbenzthiazole.*

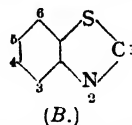
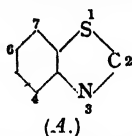
By M. A. THOROLD ROGERS and W. A. SEXTON.

2:2'-Diaminodiphenyl disulphide condenses with ethyl acetoacetate to give 3-keto-2-acetyl-2:3-dihydrobenzthiazine (IV) and 2-acetonylbenzthiazole (V) (with its derived 2-methylbenzthiazole) in approximately equimolecular proportion. Zinc and acetic acid convert (IV) into (V) and sodium hydroxide hydrolyses it to 3-keto-2:3-dihydrobenzthiazine (VI). A similar series is derived from ethyl benzoylacetate. Mechanisms are suggested.

THE formation of 2-acetonylbenzimidazole by condensation of *o*-phenylenediamine with ethyl acetoacetate or by reduction of acetoacet-*o*-nitroanilide has been demonstrated by one of us (Sexton, *J.*, 1942, 303) and its ability to couple with diazonium salts prompted us to investigate the analogous benzthiazole derivative (V).

2:2'-Dinitrodiphenyl disulphide was reduced by iron in alcohol to the diamine, this method giving, in contrast to those hitherto recorded, satisfactory yields of pure material with little trouble. Condensation with ethyl acetoacetate in chlorobenzene gave three products, 2-acetonylbenzthiazole (V) (26.7%), 2-methylbenzthiazole (VII) (21.6%), and 3-keto-2-acetyl-

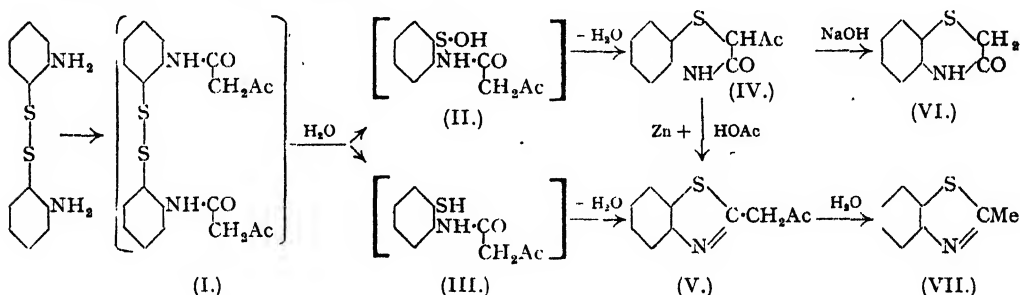
* The numbering of the benzthiazole system (A) here follows what is now the usual practice. In



earlier papers of this series (*J.*, 1939, 470, 473; 1942, 304; 1944, 11) the Richter numbering (B) was used.—EDITOR.

2 : 3-dihydrobenzthiazine (IV) (43%), together with water. The structure of the new compounds was established as follows.

The substance (IV), which crystallised from the chlorobenzene on cooling, and which *a priori* might be expected to be the bis-*N*-acetoacetyl derivative (I) of diaminodiphenyl disulphide, was shown to have a molecular weight of half that required for this structure. Since the possibility of dissociation of (IV) during the molecular-weight determination could not be excluded, and since analysis fails to differentiate between the thiazine and the disulphide structures, (IV) and (I), respectively, a chemical method was sought and found in the action of *N*-sodium hydroxide; for on dissolving in this reagent and being warmed, the whole material was rapidly converted into 3-keto-2 : 3-dihydrobenzthiazine (VI) and acetic acid, the latter being determined by titration. This is easily explained on the basis of the thiazine formula (IV) as hydrolysis, whereas the disulphide structure could give only half the amount of each of these (unless atmospheric oxygen was absorbed, and this was excluded by showing that the reaction is not affected by the absence of air, or by the presence of reducing agents); for the hydrolytic fission of disulphides leads to the formation of equimolecular quantities of thiols and sulphenic acids (see Gilman, "Organic Chemistry", 1942, 2nd Ed., Vol. II, p. 863) and only the sulphenic acid moiety is able to give 3-keto-2 : 3-dihydrobenzthiazine and acetic acid. Other properties of the substance (carbonyl activity, coupling of freshly prepared alkaline solutions with diazonium salts) are as readily understood on the basis of the formula (IV) as on the basis of the disulphide structure (I).



The structure of the other new product of the condensation, (V), presented little difficulty. It was soluble in both acids and alkalis, and the alkaline solution coupled with diazonium solutions; it showed carbonyl activity (2 : 4-dinitrophenylhydrazone) and gave an isonitroso-derivative; and its alkaline solution decomposed rapidly on heating to give 2-methylbenzthiazole. Finally, it was made in good yield from (IV) by reduction with zinc dust and acetic acid, which might be expected if (IV) is considered as a cyclic derivative of acetoacetanilide; the thiol (III) is a probable intermediate.

It is not difficult to postulate a reasonable mechanism for the formation of the three products of the acetoacetic ester condensation. It may be supposed that the bisacetoacetyl derivative (I) of the diamine is the first product, and that this is hydrolysed by traces of water, which may be present initially in the reagents, or may be formed by a Schiff's base type of side reaction. Such a neutral hydrolysis of the disulphide link is not usually considered to take place, but Schöberl and Eck (*Annalen*, 1936, 522, 97) have shown that it is probable that the reaction $-S-S- \rightleftharpoons -SH + -S\cdot OH$ is reversible, with equilibrium much on the side of the disulphide; provided that irreversibility is ensured, in their case by loss of hydrogen sulphide, the hydrolysis can go to completion. We picture the thiol (III) as being removed as soon as it is formed by ring closure to (V), while the sulphenic acid (II) is likewise converted into (IV). The water which is formed in each of these processes is available for further hydrolysis of the disulphide link, and the reaction becomes autocatalytic. Some of the thiazole (V) is hydrolysed during the reaction or during the subsequent steam distillation to methylbenzthiazole, so the combined yields of this and of (V) approach the theoretical of 50%, as does that of (IV).

Similar results were obtained in a brief investigation of the analogous series from ethyl benzoylacetate; 3-keto-2-benzoyl-2 : 3-dihydrobenzthiazine and 2-phenacylbenzthiazole were made in this way.

EXPERIMENTAL.

2 : 2'-Diaminodiphenyl Disulphide.—2 : 2'-Dinitrodiphenyl disulphide (100 g.; the sulphide made as described in *Org. Synth.*, Coll. Vol. I, p. 215, is satisfactory, provided that all inorganic sulphur be

removed by thorough washing with water) was added to a mixture of boiling alcohol (95%; 2 l.) and iron filings (200 g.), to which had been added concentrated hydrochloric acid (10 c.c.) 30 mins. previously. The mixture was heated under reflux for 16 hours in a water-bath in an apparatus fitted with efficient mechanical stirring, and was then filtered hot through a kieselguhr bed and concentrated to 600 c.c. On cooling, the diamine (60 g.; 76%) separated as yellow plates, m. p. 90–92°. One recrystallisation from alcohol (charcoal) gave material of better colour, m. p. 93–93.5°.

3-Keto-2-acetyl-2:3-dihydrobenzthiazine (IV).—The foregoing diamine (12.4 g.), dissolved in warm chlorobenzene (50 c.c.), was added during $\frac{1}{2}$ hr. to a boiling solution of ethyl acetoacetate (14.5 c.c.) in chlorobenzene (75 c.c.). The clear yellow liquid was distilled until wet chlorobenzene (80 c.c.) had been collected. To the residue was added further chlorobenzene (50 c.c.), and the same amount was distilled over. The process was repeated, no more water then appearing in the distillate. The residue was kept overnight, and the pale yellow prisms were collected and washed with light petroleum (b. p. 40–80°) (8.9 g., 43%); recrystallisation (charcoal) from alcohol or toluene gave large, colourless prisms, m. p. 164–164.5° (Found: C, 57.9; H, 4.35; N, 6.75; S, 16.1; M, Rast, 189. $C_{10}H_9O_2NS$ requires C, 57.95; H, 4.35; N, 6.75; S, 15.5%; M, 207). 2:4-Dinitrophenylhydrazones, mustard-yellow micro-needles from toluene, m. p. 242–243° (decomp.) (Found: C, 49.9; H, 3.8. $C_{18}H_{13}O_6N_5S$ requires C, 49.6; H, 3.4%).

2-Acetonylbenzthiazole (V).—(a) *From the ethyl acetoacetate condensation.* The filtrates from the foregoing experiment were subjected to steam distillation; after the chlorobenzene had distilled, the subsequent cloudy distillate had a smell like that of pyridine; about 600 c.c. of this were collected. The yellow oil remaining from the steam-distillation solidified on standing. After one crystallisation from alcohol it gave yellow plates (1.55 g.), m. p. 113–115°. Recrystallisation from alcohol gave colourless plates, m. p. 122° (Found: N, 7.55. $C_{10}H_9ONS$ requires N, 7.35%). The distillate was acidified (hydrochloric acid), whereupon the oily material passed into solution, leaving a little solid which was removed by filtration and identified as 2-acetonylbenzthiazole (0.2 g.; total yield 26.7%). The filtrate was basified to Clayton-yellow with sodium hydroxide, and extracted with ether, and the ether removed by distillation, leaving 2-methylbenzthiazole (1.8 g.; 21.6%), identified as its picrate, m. p. 153–155° (lit. m. p. 152–153°).

(b) *From 3-keto-2-acetyl-2:3-dihydrobenzthiazine (IV).* To the thiazine (5.2 g.) in boiling acetic acid (150 c.c.) was added zinc dust (8 g.) during 10 mins. After refluxing for a further $\frac{1}{2}$ hour, the solution was filtered and cooled, and water was added, precipitating 2-acetonylbenzthiazole (II) as colourless plates (4.2 g., 87.5%), m. p. 122°.

It decolourised bromine in carbon tetrachloride solution; its solutions in cold 2N-sodium hydroxide gave yellow azo-compounds with diazonium solutions; on boiling the alkaline solution, an oil, with a pyridine-like smell, separated after a few minutes, and was extracted with ether, dried over sodium hydroxide, and the ether removed. Addition of alcoholic picric acid to an alcoholic solution of the residue gave the picrate of 2-methylbenzthiazole, m. p. 153–155°. 2-Acetonylbenzthiazole was soluble in hot 2N-hydrochloric acid; on cooling, the hydrochloride separated as colourless needles, m. p. 200° (from 2N-hydrochloric acid or from alcohol). Treatment of a suspension of the hydrochloride in dilute hydrochloric acid with sodium nitrite solution until a permanent starch-iodine reaction was obtained gave pale yellow isonitroso-2-acetonylbenzthiazole, long yellow needles, m. p. 152–152.5° (from alcohol) (Found: C, 54.7; H, 3.6. $C_{10}H_8O_2N_2S$ requires C, 54.55; H, 3.6%).

Action of Alkali on 3-Keto-2-acetyl-2:3-dihydrobenzthiazine (IV).—The thiazine (2.08 g.) was dissolved in boiling N-sodium hydroxide (20 c.c.). After about 3 mins. there separated long needles of 3-keto-2:3-dihydrobenzthiazine (VI); after a further $\frac{1}{2}$ hour at 100°, the suspension was cooled and N-hydrochloric acid (30 c.c.) was added; the solution was filtered through a weighed IG3 sintered-glass Gooch funnel. The ketodihydrothiazine (VI) was washed with water, dried at 100°, and weighed; 1.66 g. (100%); m. p. 179° (not depressed by mixture with an authentic specimen) (Found: N, 8.4; S, 19.4. Calc. for C_8H_7ONS : N, 8.5; S, 19.4%). The yield was not lowered by conducting the reaction in an atmosphere of nitrogen or by the presence of sodium sulphide in the alkaline solution.

A further portion of the thiazine (2.08 g.) was treated with 0.975N-sodium hydroxide (20 c.c.) in the same way; the cooled alkaline suspension was filtered, and the residue washed well with water. Titration of the filtrate, using phenolphthalein, with hydrochloric acid (10 c.c. of 0.929N) shows, by difference, a weak acid content of 1.02 mols. per mol. of thiazine. Similar results were obtained when the hydrolysis was conducted in an atmosphere of nitrogen.

(IV) (2.0 g.) was recovered unchanged (1.5 g.) when its solution in alcohol (20 c.c.) was heated under reflux with 2N-hydrochloric acid (5 c.c.) for 6 hours.

3-Keto-2-benzoyl-2:3-dihydrobenzthiazine.—This was made from ethyl benzoylacetate (42.4 g.) and diaminodiphenyl disulphide (24.8 g.) in chlorobenzene (250 c.c.) as described for (IV); it formed large lemon-yellow prisms, m. p. 188° (Found: C, 66.55; H, 4.0; N, 5.05; M, Rast, 242. $C_{15}H_{11}O_2NS$ requires C, 66.9; H, 4.1; N, 5.2%; M, 269). It formed yellow solutions in hot N-sodium hydroxide which faded on boiling with quantitative formation of the thiazine (VI); acidification of the filtrate gave benzoic acid (m. p. and mixed m. p.). 2-Phenacylbenzthiazole, made by zinc dust reduction of the foregoing compound in acetic acid, formed needles from benzene, m. p. 150° (Found: N, 5.6. $C_{13}H_{11}ONS$ requires N, 5.55%).

323. The Polysaccharides of Carragheen. Part II. The *Gigartina stellata* Polysaccharide.

By ERIC T. DEWAR and E. G. V. PERCIVAL.

The water-soluble polysaccharide of *Gigartina stellata* is shown to resemble the *Chondrus crispus* polysaccharides. Crystalline 2:6-dimethyl β -D-galactose has been isolated by the hydrolysis of the methylated polysaccharide.

ALTHOUGH some authorities ("British Pharmaceutical Codex", London, 1934, p. 320; "Thorpe's Dictionary of Applied Chemistry", Longmans, 4th. Edn. 1937, p. 199) appear to reserve the term carragheen for the red alga *Chondrus crispus*, and it was used in this sense in Part I (J., 1943, 51), others, for example Tseng (*Science*, 1945, 101, 2633) and Newton (*Endeavour*, 1945, IV, 14, 69) also include *Gigartina stellata*, Batt. in this description on account of the close morphological resemblances between the two algae. It is not surprising therefore that the polysaccharides extracted by hot water from these two red seaweeds prove, as the present investigation shows, to be of the same type.

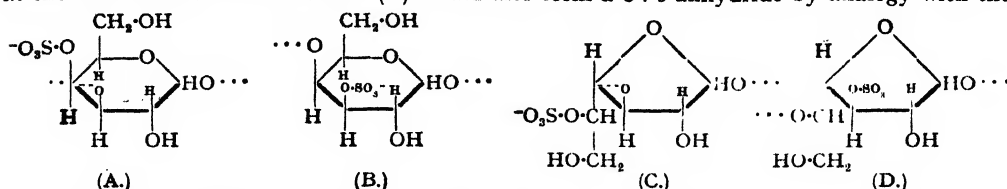
The polysaccharide obtained by the extraction of *Gigartina stellata* with hot water mainly as the calcium salt, but containing in addition magnesium, sodium, and potassium, gave D-galactose (40%) on hydrolysis, and had $[\alpha]_D^{25} + 51^\circ$ in water (SO_4 , 23.9%); the hot extract from *Chondrus crispus* had $[\alpha]_D^{25} + 63^\circ$ (SO_4 , 23.8; galactose 36.9%) (J., 1943, 51). In its stability to sodium hydroxide (N) at 100° the polysaccharide also resembled the *Chondrus* extracts, three days being necessary to remove 62% of the sulphate residues. The free acid polysaccharide was isolated ($[\alpha]_D^{25} + 43^\circ$; SO_4 , 25.9%; neutralisation equivalent, 371) and potentiometric titration showed it to be a typically strong acid. Acetylation was accomplished by a modification of the method of Pacsu and Mullen (*J. Amer. Chem. Soc.*, 1941, 63, 1487), deacetylation and methylation of the acetate (CH_3CO , 19.1%) giving a partially methylated polysaccharide (OMe, 16.2%) from which after repeated methylation with sodium hydroxide and methyl sulphate a product, $[\alpha]_D^{25} + 43^\circ$ (OMe, 18.6; Ca, 3.8; Mg, 0.9; SO_4 , 24.7%), was obtained, the retention of the ethereal sulphate emphasising the stability of that grouping to alkali.

Hydrolysis of the methylated polysaccharide gave a crystalline dimethyl galactose which was identified as 2:6-dimethyl galactose as follows. Oxidation gave a crystalline dimethyl galactonic acid which on distillation yielded a lactone, proved to be a γ -lactone because of its slow hydrolysis in water. A free hydroxyl group was therefore present on C_4 , and this fact was confirmed by the inversion of the sign of rotation of the free sugar on methylgalactofuranoside formation. The amide prepared from the lactone gave a negative Weerman test, proving substitution by methoxyl on C_2 , a fact confirmed on osazone formation since 6-methyl galactosazone (Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, 60, 324) was obtained. Proof of the substitution of the primary alcohol residue by methoxyl was afforded by the fact that no iodine entered the molecule when the ditosyl dimethyl methylgalactoside was treated with sodium iodide in acetone (Oldham and Rutherford, *ibid.*, 1932, 54, 366). The isolation of a crystalline dimethyl monoacetone β -methylgalactopyranoside also proved the presence of free hydroxyl groups on C_3 and C_4 .

The only fact at variance with the proposed assignment of structure was that, although the specific rotations were almost identical, the melting point of 131° for 2:6-dimethyl galactose recorded by Oldham and Bell (*loc. cit.*) was much higher than the value ($119\text{--}120^\circ$) we obtained for our crystalline dimethyl galactose. The facts were re-examined by Dr. D. J. Bell (J., 1945, 692) who repeated and extended the earlier work, and mixed melting point determinations of our dimethyl galactonic acid phenylhydrazide with the corresponding derivative prepared from 2:6-dimethyl galactose, the structure of which had been proved unequivocally both by the synthetic route employed and by periodate oxidation, showed no depression. Furthermore satisfactory agreement was obtained in respect of the melting points of the dimethyl β -methylgalactoside and the corresponding 3:4-monoacetone derivative. It may be recalled that evidence was presented (Part I, *loc. cit.*) that the syrupy dimethyl galactose produced on hydrolysing the methylated *Chondrus crispus* polysaccharides was also 2:6-dimethyl galactose. In these polysaccharide sulphates, therefore, the exposed hydroxyl groups on the galactose residues are on C_2 and C_4 . If we assume that the sulphate groups are directly attached to the galactose residues four possible formulæ must be considered (see opposite page).

It has been shown recently (Percival and Duff, *Nature*, 1946, 158, 29) that barium 3-methyl 1:2-monoacetone glucufuranose 6-sulphate is readily transformed into the corresponding 5:6-anhydride by sodium methoxide. It is highly probable therefore that the sulphate groups

in (B), (C), and (D) would be readily eliminated by alkali, with formation of ethylene oxide rings in the first instance. In addition (B) would also form a 3 : 6-anhydride by analogy with the



methylglucufuranoside 3-sulphates (J., 1945, 119). The most likely arrangement is therefore (A) in which the galactopyranose residues are linked through the 1 and 3 positions as in agar, and it may be that this type of linkage is typical of the galactans of the red seaweeds. The above arguments, based on the resistance to hydrolysis with alkali of the sulphate groups, apply only if these residues are directly attached to the galactose units. It is conceivable, however, that the sulphate groups are attached to those building units (X) of the molecule which have not, as yet, been identified, with these units (X) interposing between the sulphate groups and the triply linked galactose residues. This point could be decided by removing the sulphate groups and following this by methylation, but attempts to remove the sulphate residues have been unsuccessful so far and it seems that a final decision must await the identification of (X).

The substance, or mixture of substances, (X) is clearly not a simple hexose since the methoxyl content of the methylated polysaccharide is only slightly higher than would be required for the dimethyl galactose residues found, and it will be surprising if it contains more than one free hydroxyl group. That (X) might be an anhydro- or a deoxy-sugar has not been lost sight of, but the decomposition it undergoes under acid hydrolytic conditions has prevented progress so far. The hydrolysis of the methylated polysaccharide with methanolic hydrogen chloride was unexpectedly difficult, and only derivatives of methylated galactose could be identified among the products of hydrolysis. In the case of the *Chondrus crispus* polysaccharide, Young and Rice (*J. Biol. Chem.*, 1946, **164**, 35) have isolated diacetone 2-ketogluconic acid in small yield on hydrolysis and treatment with acetone and copper sulphate, but we have not yet succeeded in isolating this material from either the *Chondrus* or the *Gigartina* polysaccharides.

EXPERIMENTAL.

Preparation of the Polysaccharide.—The air-dried seaweed, kindly supplied by Dr. A. P. Orr of the Marine Station, Millport, was washed in muslin bags in 500 g. lots with running water for 10 days. Repeated extraction with water on the steam-bath followed until the extracts were no longer appreciably viscous. The combined extracts were filtered hot and concentrated at 50°/15 mm. to small volume, and the brown viscous solution was added slowly, with mechanical stirring, to ethanol. The white fibrous material was dehydrated with fresh ethanol, washed with ether, and dried in a vacuum desiccator. For all quantitative work the substance was purified by dialysis against running water for six days, filtered, concentrated, reprecipitated, and dried over phosphoric oxide at 50°/15 mm. to constant weight. The product was neutral, non-reducing and had $[\alpha]_D^{25} + 51^\circ$ (c, 0.5 in water) [Found: Ash (as sulphate), 17.6; Ca, 3.6; Mg, 1.0; Na, 0.2; K, 0.1; SO_4 , 23.9%].

Isolation of the Acid Polysaccharide.—The polysaccharide (hereafter designated H.E.) (0.75 g.) in water (50 c.c.) was treated with hydrochloric acid to bring the concentration to N, and the solution in a cellophane bag was dialysed against hydrochloric acid (N) until free from calcium (9 days). Dialysis was continued against distilled water until free from chloride (5 days), and the solution was then diluted to 250 c.c. in a standard flask. By titration against sodium hydroxide (0.05N) to phenolphthalein, the solution was found to be 7.49×10^{-3} N; by weighing the sodium salt obtained on evaporation the equivalent of the sodium salt was calculated as 393 and that of the free acid as 371. The solution of the acid was non-reducing, but became reducing on heating at 100° for 10 minutes; $[\alpha]_D^{25} + 43^\circ$ (c, 0.14 in water) (Found: SO_4 , 25.9%).

Potentiometric Titration.—The table shows a comparison between the titration of the above acid solution (a) against sodium hydroxide (8.22×10^{-3} N) and hydrochloric acid (5.67×10^{-3} N), (b) against sodium hydroxide (5.13×10^{-3} N) using a quinhydrone electrode.

	NaOH added	e.m.f.	pH.		NaOH added	e.m.f.	pH.
	(c.c.).	(mv.).			(c.c.).	(mv.).	
a)	—	308	2.58	b)	—	304	2.65
	10	304	2.65		10	302	2.69
	20	296	2.79		20	298	2.76
	30	284	3.00		30	292	2.86
	35	270	3.24		40	280	3.07
	40	242	3.73		44	268	3.28
	43	182	4.77		46	258	3.45
	46	12	7.71		50	232	3.90
					52	160	5.15
					54	70	6.71
					56	8	7.78

Hydrolyses of H.E.—(1) H.E. (4.98 g.) was hydrolysed at 100° with oxalic acid (210 c.c.; 0.5N) to constant rotation (26 hours, $[\alpha]_D^{25} + 25^\circ$). The solution was decolorised with charcoal, neutralised with calcium carbonate, filtered, and evaporated at 35°/15 mm. to a syrup admixed with calcium sulphate. Extraction with small quantities of water, filtration, and evaporation gave a syrup (4.52 g.). Galactose was determined quantitatively by dissolving the syrup in water (45 c.c.), adding ethanol (45 c.c.), acetic acid (0.5 c.c.), and phenylmethylhydrazine (3.75 c.c.), and keeping at 0° for 4 days. The crystalline galactose phenylmethylhydrazone was filtered off, washed with water, ethanol, and ether, and dried for 3 days in a vacuum over phosphoric oxide, m. p. 186—187° (3.055 g.). Under identical conditions *d*-galactose (3.219 g.) gave galactose phenylmethylhydrazone, m. p. 186° (4.978 g.), *i.e.*, galactose from H.E., 39.6%.

(2) H.E. (11.1 g.) gave galactose phenylmethylhydrazone (6.83 g.), *i.e.*, galactose from H.E., 39.9%.

(3) H.E. (10.23 g.) was heated at 100° with a mixture of oxalic acid (0.1N) and potassium oxalate (400 c.c.; 0.1N) for 26 hours in a nitrogen atmosphere after Young and Rice (*loc. cit.*) and the procedure described by those authors for the isolation of diacetone 2-ketogluconic acid from Irish moss carried out. No identifiable products apart from galactose were obtained.

The filtrates from (1) and (2) were treated with benzaldehyde according to Lüttke (*Biochem. Z.*, 1929, 419) to yield a glass, $[\alpha]_D \pm 0^\circ$ in water, which reduced Fehling's and Barfoed's solution, gave Schiff's test, the Seliwanoff, Bredereck, and selenium dioxide ketose reactions, and the iodoform reaction in the cold; tests for pentoses, methylpentoses, and uronic acids were negative. Salts of organic acids were present, but attempts to isolate esters by treating the free acids with diazomethane followed by methylation were not successful.

Hydrolysis of H.E. with *N*-Sodium Hydroxide at 100°.—H.E. (1.521 g.) was heated with *N*-sodium hydroxide (200 c.c.) at 100° in the presence of barium chloride (1.533 g.). At definite intervals samples (25 c.c.) were withdrawn, water (25 c.c.) and dilute acetic acid (10 c.c.) added, and the solution centrifuged. The residual combined sulphate in 50 c.c. of the solution was then determined by hydrolysis with hydrochloric acid and weighing the barium sulphate produced.

Time, hrs.	4	10	32	56	72
Residual sulphate (BaSO ₄ , mg.)	70.2	65.6	47.4	38.0	34.4
Hydrolysis, %	23	28	48	58	62

Acetylation of H.E.—To H.E. (15.9 g.) dissolved in water (200 c.c.), pyridine (700 c.c.) was added, and the pyridine-water azeotrope distilled off at 50°/15 mm. (Pacsu and Mullen, *loc. cit.*) to a volume of about 250 c.c. To the brown jelly so obtained pyridine (50 c.c.) and acetic anhydride (200 c.c.) were added, slowly, with shaking and cooling. After 12 days at room temperature the acetate was separated at the centrifuge and washed with pyridine, ethanol, and ether. The white powder (18 g.) so produced had $[\alpha]_D^{25} + 46^\circ$ (*c.* 0.8 in water) (Found: CH₃CO, 19.1%).

Deacetylation and Methylation.—The above acetate in water (300 c.c.) was treated with methyl sulphate (120 c.c.) and sodium hydroxide (300 c.c.; 30%) in one-twelfth portions every ½ hour, the temperature being kept below 20°. The solution was then heated to 80° for 30 minutes, cooled, neutralised with acetic acid, and dialysed against running water until sulphate-free (10 days). The dialysed solution was evaporated at 45°/15 mm. to a glass (OMe, 16.2%). This glass was taken up in water (100 c.c.), worked up with pyridine as described above, and reacylated (CH₃CO, 5.9%). Simultaneous deacetylation and methylation as before increased the methoxyl content to 17.2%. This was followed by a third acetylation (CH₃CO, 4.4%) and methylation (OMe, 17.6%), and a fourth acetylation (CH₃CO, 3.5%) and methylation (OMe, 18.2%) (14 g.).

Attempts to increase the methoxyl content of this specimen by three direct methylations with methyl sulphate and sodium hydroxide in the usual way were unsuccessful, as was the application of the thallium method (Hirst *et al.*, *J.*, 1939, 1884).

The methylated polysaccharide was obtained by precipitation from aqueous solution (after dialysis) by ethanol, as a white fibrous solid, $[\alpha]_D^{25} + 43^\circ$ (*c.* 1.6 in water) [Found: Ash (as sulphate), 18.2; Ca, 3.75; Mg, 0.94; Na, 0.31; SO₄, 24.7; OMe, 18.6%].

Hydrolysis of the Methylated Polysaccharide.—The above product (5.13 g.; OMe, 18.6%) was hydrolysed at 100° with oxalic acid (200 c.c., *N*/2) until the rotation was constant ($[\alpha]_D^{25} + 37^\circ$). The solution was neutralised with calcium carbonate and worked up in the usual way to a brown syrup (4.0 g., OMe, 26.3%).

Glycopyranoside Formation.—This syrup was boiled with methanolic hydrogen chloride (160 c.c.; 6%) until non-reducing (8 hours), neutralised with silver carbonate, evaporated, and extracted with ether to give a syrup (2.34 g., OMe, 36.0%, $n_D^{25} 1.4865$) which was fractionated to give (1) 0.09 g., b. p. 100°/0.1 mm., $n_D^{25} 1.4295$; (2) 1.9 g., b. p. 145—155°/0.07 mm., $n_D^{25} 1.4737$, $[\alpha]_D^{25} + 70^\circ$ (*c.* 1.4 in water) (Found: OMe, 40.4. Calc. for C₆H₁₂O₆: OMe, 41.9%). Fraction (1) was identified as methyl laevulate isolated as the dinitrophenylhydrazone, m. p. 136° not depressed on admixture with an authentic specimen.

Preparation of Tetramethyl *d*-Galactopyranose Anilide from (2).—Fraction (2) (0.57 g.) was methylated with methyl sulphate and sodium hydroxide followed by two treatments with Purdie's reagents to give a mobile syrup (0.47 g.), distilled, 90—110°/0.02 mm., to yield a colourless liquid (0.4 g.; $n_D^{25} 1.4495$) which was hydrolysed with sulphuric acid (15 c.c., *N*) at 100° for 6 hours. From the reducing syrup (0.35 g.) isolated in the usual way, treatment with aniline in alcohol gave an anilide (0.23 g., m. p. 193—194°, not depressed by authentic tetramethyl galactopyranose anilide; $[\alpha]_D^{25} - 80^\circ$ (*c.* 0.6 in acetone).

Isolation of Crystalline Dimethyl Galactose.—Fraction (2) (0.81 g.) was hydrolysed with sulphuric acid (30 c.c.; *N*) for 5 hours, $[\alpha]_D^{25} + 82^\circ$. Neutralisation with barium carbonate, filtration, and evaporation gave a crystalline product (0.65 g.), m. p. 119—120° after three recrystallisations from dry ethyl acetate, $[\alpha]_D^{25} + 48^\circ$ (10 mins.), + 87° (240 mins., constant; *c.* 0.67 in water) (Found: C, 46.5; H, 7.5; OMe, 29.1. Calc. for C₆H₁₂O₆: C, 46.2; H, 7.7; OMe, 29.8%). Normally crystallising as needles, this

dimethyl galactose was obtained in the form of large plates from ethyl acetate–light petroleum (b. p. 40–60°).

Isolation of 6-Methyl Galactosazone.—The free sugar (0.34 g.) in water (5 c.c.) gave several crops (0.26 g.) of an osazone which on recrystallisation had m. p. 201–203° not depressed by authentic 6-methyl galactosazone (Found: OMe, 7.1. Calc. for $C_{10}H_{24}O_4N_4$: OMe, 8.3%).

Galactofuranoside Formation.—The sugar in methanolic hydrogen chloride (1%; c, 1.675) showed the following rotational changes (time in hours): $[\alpha]_D^{25} + 42^\circ$ (0.75); 23° (18); 12.5° (25); – 9.5° (42); – 15.5° (48); – 29° (66); – 39° (92); – 43° (114; constant).

Evidence for Substitution on C₆.—Fraction (2) was treated with an excess of toluene-*p*-sulphonyl chloride in pyridine to yield a syrupy product, $[\alpha]_D^{25} + 32^\circ$ (c, 2.3, in chloroform) (Found: OMe, 15.5. $C_{10}H_{20}O_5S_2$ requires OMe, 17.6%).

Treatment with sodium iodide in acetone according to Oldham and Rutherford (*loc. cit.*) gave a product devoid of iodine. Oxidation of the crystalline dimethyl galactose with sodium periodate gave no formaldehyde.

Derivatives of 2:6-Dimethyl Galactose.—2:6-Dimethyl galactonic acid. The dimethyl galactose (1.59 g.) in water (25 c.c.) was treated with bromine (1.75 c.c.) at room temperature until non-reducing (6 days). After aeration, neutralisation with silver carbonate, and treatment with hydrogen sulphide, etc., a viscous syrup (1.66 g.), $[\alpha]_D^{25} + 26^\circ$ (c, 1.6 in water), was obtained (Found: C, 42.5; H, 7.1; OMe, 24.8. $C_8H_{14}O_7$ requires C, 42.9; H, 7.2; OMe, 27.7%).

2:6-Dimethyl γ -galactonolactone. The above crystalline acid (0.96 g.) distilled at 180°/0.02 mm. to give a syrup (0.9 g.), $n_D^{20} 1.4760$, $[\alpha]_D^{25} - 49^\circ$ (initial); – 24° (28 days; c, 1.09 in water) (Found: OMe, 28.6; equiv., 205. Calc. for $C_8H_{14}O_6$: OMe, 30.1%; equiv., 206). Titration with sodium hydroxide was characteristic of a γ -lactone.

2:6-Dimethyl galactonamide. The above lactone (0.34 g.) was treated with methanolic ammonia (5 c.c.) at 0° for 2 days; removal of solvent gave a crystalline amide (0.365 g.) which after three recrystallisations from ethanol gave small needles, m. p. 154–155°, $[\alpha]_D^{25} + 46^\circ$ (c, 0.85, in water) (Found: C, 43.5; H, 7.3; N, 6.0; OMe, 26.7. $C_{10}H_{21}O_5N$ requires C, 43.1; H, 7.7; N, 6.3; OMe, 27.8%). This amide (0.1 g.) gave a negative Weerman reaction.

2:6-Dimethyl galactonic acid phenylhydrazide. The lactone (0.2 g.) was allowed to react with phenylhydrazine (1 mol.) in boiling ether for 15 minutes. On removing the solvent and heating at 85–90° for 2 hours, a crystalline product was obtained which was recrystallised (0.25 g.) from ethanol–ether, m. p. 140° alone and admixed with an authentic specimen of 2:6-dimethyl galactonic acid phenylhydrazide supplied by Dr. D. J. Bell (Found: C, 53.1; H, 7.2; N, 8.9; OMe, 19.0. Calc. for $C_{14}H_{23}O_5N_2$: C, 53.5; H, 7.1; N, 8.9; OMe, 19.8%).

2:6-Dimethyl β -methyl- α -galactoside. The dimethyl galactose (0.5 g.) was acetylated at room temperature with pyridine and acetic anhydride in the usual way to give a crystalline acetate which was treated with hydrogen bromide in acetic acid followed by silver carbonate and methanol to give a non-reducing syrup (0.66 g.), $[\alpha]_D^{25} + 19^\circ$ (c, 6.6 in chloroform). This was deacetylated with sodium hydroxide (0.1N) and the product distilled at 145–150°/0.05 mm. to give a syrup (0.38 g.), $n_D^{20} 1.4763$, which crystallised on standing. After two recrystallisations from ether–light petroleum (b. p. 40–60°), hygroscopic needles, m. p. 72°, were obtained, $[\alpha]_D^{25} - 22^\circ$ (c, 0.9 in chloroform) (*cf.* Bell, *loc. cit.*) (Found: OMe, 41.0. Calc. for $C_9H_{17}O_6$: OMe, 41.9%).

2:6-Dimethyl 3:4-monoacetone β -methylgalactoside. The mother liquors from the above recrystallisations were evaporated to a syrup which crystallised slowly (0.2 g.) and was dissolved in dry acetone (50 c.c.) and shaken for 4 days with anhydrous copper sulphate (2 g.). After the usual treatment, distillation at 100°/0.1 mm. gave a crystalline product, m. p. 55° (*cf.* Bell, *loc. cit.*) (Found: OMe, 34.5. Calc. for $C_{12}H_{22}O_6$: OMe, 35.5%).

2:6-Dimethyl galactose anilide. The dimethyl galactose (0.31 g.) in ethanol (7 c.c.) was heated with aniline (1 mol.) at 80° for 3.5 hours to give a crystalline anilide (0.42 g.). Three recrystallisations from ethanol gave needles, m. p. 121–122°, $[\alpha]_D^{25} + 15^\circ$ (c, 0.7 in ethanol) (Found: N, 5.2; OMe, 22.2. $C_{14}H_{21}O_5N$ requires N, 4.9; OMe, 21.9%). A satisfactory elementary analysis for carbon could not be obtained from this material (*see also* Bell, *loc. cit.*).

Hydrolysis of Methylated H.E. followed by Furanoside Formation.—Methylated H.E. (5.23 g.; OMe, 18.6%) was hydrolysed with oxalic acid (0.5N) as before to give a syrup (3.54 g.) which was treated with methanolic hydrogen chloride (100 c.c.; 2%) at room temperature. After 8 days the solution was non-reducing ($[\alpha]_D^{25} - 30^\circ$ (c, 0.7)). Neutralisation with silver carbonate, etc., gave a syrup (2.75 g.) which was distilled in the presence of barium carbonate, giving: (1) 0.05 g., b. p. 100°/15 mm., $n_D^{20} 1.4302$; (2) 1.98 g., b. p. 120–145°/0.04 mm., $[\alpha]_D^{25} - 35^\circ$ (c, 3.8; in water), $n_D^{20} 1.4672$ (OMe, 39.0%); (3) 0.3 g., b. p. 145–165°/0.02 mm., $n_D^{20} 1.4710$; (4) 0.13 g., b. p. 165–205°/0.02 mm., $n_D^{20} 1.4813$, $[\alpha]_D^{25} - 8^\circ$ (c, 1.1 in water) (OMe, 33.9%). Fraction (2) was a mixture of 2:6-dimethyl methylgalactofuranosides and gave on hydrolysis (1.66 g.) crystalline 2:6-dimethyl galactose (1.2 g.), m. p. 110° without recrystallisation. Fraction (4) was thought to be an impure monomethyl methylgalactoside, but attempts to secure evidence of this by osazone formation were not successful.

Hydrolysis of Methylated H.E. with Methanolic Hydrogen Chloride.—Methylated H.E. (4.65 g.; OMe, 20.2%) was heated with methanolic hydrogen chloride (200 c.c.; 1.2%) for 24 hours in the presence of barium chloride (5.1 g.). After neutralisation with barium carbonate a non-reducing glass (4.1 g.) was isolated which still contained sulphur (OMe, 33.5%); this was boiled for 16 hours with methanolic hydrogen chloride (100 c.c.; 2%) in the presence of barium chloride. After neutralisation and suitable treatment an ether-soluble fraction (A) (1.15 g.) and a glass (B) (2.6 g.) were isolated. (B) was further hydrolysed for 24 hours with methanolic hydrogen chloride (100 c.c.; 2.7%) and barium chloride from which an ether-soluble fraction (C) (0.23 g.) and an ethanol-soluble fraction (D) (2.1 g.; OMe, 32.0%) were obtained. (A) and (C) were combined and distilled at 135–155°/0.05 mm. to give mainly 2:6-dimethyl methylgalactosides (1.11 g.), $n_D^{20} 1.4748$ (OMe, 38.1%), which gave crystalline 2:6-dimethyl galactose in good yield on hydrolysis.

Fraction (D) (1.75 g.) was dissolved in methano and methylated five times with silver oxide and

methyl iodide. Distillation gave: (1) 0.79 g., b. p. 90—95°/0.02 mm., n_D^{17} 1.4481 (OMe, 57.6%); (2) 0.54 g., b. p. 95—100°/0.02 mm., n_D^{17} 1.4478 (OMe, 56.9%); (3) 0.12 g., b. p. 100—125°/0.02 mm., n_D^{17} 1.4483 (OMe, 55.3%).

Fraction (1) (0.43 g.) was hydrolysed with sulphuric acid (N) and the reducing syrup (0.3 g.) treated with aniline in ethanol to give tetramethyl *d*-galactopyranose anilide (0.14 g.), m. p. 195°, $[\alpha]_D^{16}$ — 78° (c, 0.7 in acetone). The other component of the mixture could not be identified.

Fractions (1), (2), and (3) (0.9 g.) were combined, and, after hydrolysis and treatment with aniline, tetramethyl *d*-galactopyranose anilide (0.3 g.), m. p. 196—197°, $[\alpha]_D^{18}$ — 81° (c, 0.7 in acetone), was obtained. No other products could be identified.

A further hydrolysis with methanolic hydrogen chloride (4%, in nitrogen) resulted in the isolation after a chromatographic separation on aluminium oxide of 2:6-dimethyl galactose, m. p. 112° (30%). No other identifiable products could be isolated, and a search for methylated derivatives of 2-ketogluconic acid after complete methylation was abortive.

Thanks are expressed to Dr. A. P. Orr, Marine Biological Station, Millport, for the gift of material, to Dr. D. J. Bell for specimens, and to Imperial Chemical Industries Ltd. and the Earl of Moray Endowment for grants.

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[Received, February 4th, 1947.]

324. The Reaction of $\alpha\beta$ -Ethyne Ketones with Active Methyl and Methylene Compounds.

By A. W. JOHNSON.

The reaction of acyl- or aroyl-acetylenes (2 mols.) and pyridines containing a 4-methyl or methylene group yields violet adducts which are represented by structures such as (III). An active "zwitterion" formed from 2 mols. of the ethynyl ketone is postulated as the intermediate in these and similar reactions. With 1:3:3-trimethylindolenine methiodide, the acyl- or aroyl-acetylenes give, after the addition of alkali, adducts formed from equimolecular quantities of the reactants, but the corresponding reaction with 2-methylbenzthiazole ethiodide resembles those with the pyridines in that 2 mols. of the ketone react with each mol. of base. The addition of ethynyl ketones to nitrogen heterocyclic compounds containing active methylene groups, e.g., 1-phenyl-3-methyl-5-pyrazolone, and active methine groups, e.g., 2:4-diphenylpyrrole and 2-methylindole, is also described.

In the course of other work on the reactions of the $\alpha\beta$ -ethynyl ketones, $R\cdot CO\cdot C\equiv CH$, it was observed that when phenyl ethynyl ketone (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) was dissolved in either methylated spirits or industrial absolute alcohol, a deep violet colour rapidly developed on warming, or more slowly at room temperature. This colour was not obtained with methyl alcohol or denaturant-free alcohol. A sample of alcohol denaturant was therefore obtained and fractionated, and the colour shown to be associated with the presence of pyridine bases. Attention was then turned to the reaction of individual specially purified pyridine and quinoline homologues (0.5 c.c.) with phenyl ethynyl ketone (0.05 g.) in methyl alcohol (2 c.c.), and the following colours were observed:

Base.	Purification.	Colour.
Pyridine	Fractionation	Pale yellow
α -Picoline	Regeneration from $HgCl_2$ adduct, m. p. 153—154°	Dark reddish-brown
β -Picoline	Regeneration from oxalate, ¹ m. p. 108—109°	Pale yellow
γ -Picoline	Regeneration from oxalate, ² m. p. 139—140°	Intense reddish-violet; crystals separated on standing
4-Ethylpyridine	Fractionation ³ (synthetic)	Intense reddish-violet; crystals separated on standing
2:4-Lutidine	Regeneration from $HgCl_2$ adduct, ^{1,4} m. p. 117—119°	Intense reddish-violet; no separation of solid
2:6-Lutidine	Regeneration from $HgCl_2$ adduct, ¹ m. p. 187—189°	Pale pink
Quinaldine	Fractionation	Pale yellow
Lepidine	Fractionation (synthetic)	Orange-red

¹ Lidstone, *J.*, 1940, 241.

² Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, 63, 490.

³ Wibaut and Arens, *Rec. Trav. chim.*, 1941, 60, 119.

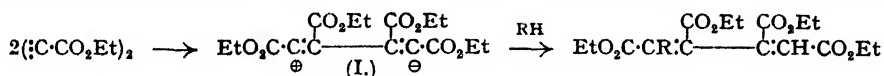
⁴ Bratton and Bailey, *J. Amer. Chem. Soc.*, 1937, 59, 177.

It was therefore apparent that the coloration observed in alcoholic solutions of phenyl ethynyl ketone was due to the presence of pyridine homologues containing active (*i.e.*, α - or γ -)

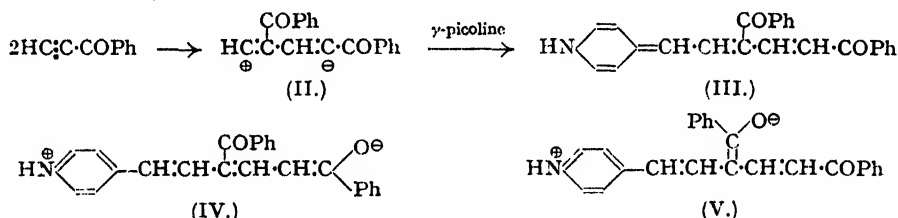
methyl or methylene groups and that violet colorations were to be particularly associated with the γ -substituted pyridines. The colour produced from the reaction of γ -picoline with phenyl ethynyl ketone proved to be sufficiently sensitive to detect 2 p.p.m. of the base in methyl alcohol. Attempts were made to apply the colour reaction to the quantitative determination of α -picoline in pyridine (γ -picoline may be readily separated from pyridine by fractionation), but the reaction proved to be less sensitive in the case of the α -isomer, and other methods for the estimation of α -picoline were found to be preferable.

Purification and analyses of the violet adduct from γ -picoline and phenyl ethynyl ketone indicated a molecular formula, $C_{24}H_{19}O_2N$ (i.e., $2C_9H_6O, C_6H_7N$), and this was supported by the almost quantitative yield of the adduct obtained on mixing 2 mols. of phenyl ethynyl ketone with 1 mol. of γ -picoline in a small volume of methyl alcohol. The same adduct was obtained when other alcoholic solvents, e.g., 2-ethoxyethanol, were used as solvents for the reaction, but in non-polar solvents such as ether or benzene mixtures of products were formed.

It is probable that the reaction of ethynyl ketones with γ -picoline and similar compounds closely resembles those described by Diels and his co-workers (*Annalen*, 1932, 498, 16; 1933, 505, 103; 1934, 510, 87; 513, 129; 1935, 516, 45; 519, 140; 1936, 525, 73; 1937, 530, 68; 1939, 543, 79; 1944, 556, 38; *J. pr. Chem.*, 1940, 156, 195; *Ber.*, 1942, 75, 1452) in which ethyl acetylenedicarboxylate was caused to react with a variety of heterocyclic bases. It was postulated that the zwitterion (I) was an intermediate which reacted with the base as shown:



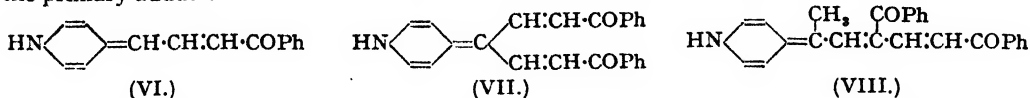
In the case of phenyl ethynyl ketone the active intermediate would be (II) by analogy, giving (III) on addition to γ -picoline:



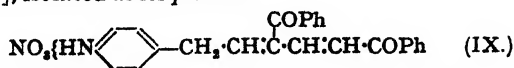
The intense violet colour of the adduct is probably due to the resonance between (III) and structures such as (IV) and (V).

A further example of phenyl ethynyl ketone reacting in the zwitterion form was encountered in the reaction with ammonium acetate in acetic acid solution, 5-benzoyl-2-phenylpyridine being obtained (cf. Bowden and Jones, *J.*, 1946, 953) together with *s*-tribenzoylbenzene.

Another possible mechanism for the reaction is that the compound (VI) is the intermediate in the reaction, in which case the final adduct could be (III) or (VII). Of the two mechanisms, the former is preferred, for it will be shown later that 2:3:3-trimethylindolenine methiodide reacts with only 1 equiv. of ethynyl ketones to give adducts of the type (VI) after the addition of potassium acetate, and in no case could a second equiv. of ethynyl ketone be induced to add to the primary adduct.

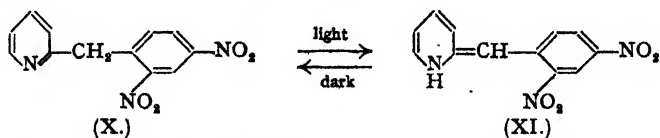


Nevertheless, structure (VII) has been eliminated on chemical grounds, for it was shown that the reaction of 4-ethylpyridine (Wibaut and Arens, *loc. cit.*) with phenyl ethynyl ketone in methanolic solution readily gave the violet adduct (VIII). The accepted structure (III) for the adduct of γ -picoline and phenyl ethynyl ketone was further supported by oxidative degradation. Oxidation with 50% nitric acid gave benzoic acid (2 mols.) and isonicotinic acid (1 mol.) [i.e., from the nitric acid salt (IX)], isolated as its *picrate*.

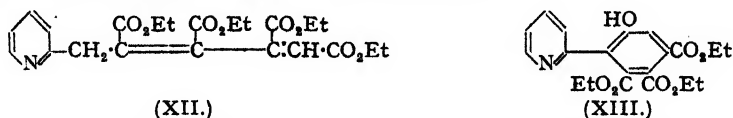


Analogues of (III) have been prepared by reaction of γ -picoline with methyl ethynyl ketone, *m*-methoxyphenyl ethynyl ketone, and *o*-chlorophenyl ethynyl ketone, severally. With phenyl

1-hexynyl ketone and γ -picoline in methanolic solution a deep blue solution was obtained but the adduct was an oil. Stable pyridine methide compounds containing no nitrogen substituents are uncommon, but Tschitchibabin, Kuindshi and Benewolenskaya (*Ber.*, 1925, 58, 1580) have shown that the yellow compound (X) is converted into the purple isomer (XI) on irradiation. The reverse change occurs in the absence of light.



Diels and Pistor (*Annalen*, 1937, 530, 87) have shown that α -picoline reacts with ethyl acetylenedicarboxylate in ethereal solution to give some of a dark red adduct formulated as (XII), which was converted into (XIII) on refluxing with methyl alcohol. No mention was made of the possibility of (XII) being in the quinonoid form.

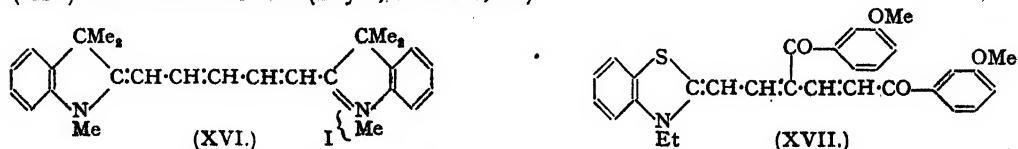


The reaction of $\alpha\beta$ -ethynyl ketones with quaternary salts containing active methyl groups has also been investigated. Phenyl ethynyl ketone with 2:3:3-trimethylindolenine methiodide, after the addition of potassium acetate to remove the elements of hydrogen iodide, gave a red crystalline compound, m. p. 158–159°, which contained no iodine, had the constitution $C_{21}H_{21}ON$, and was formulated as (XIV; R = Ph).



This formulation was supported by the almost quantitative yield of (XIV) obtained on mixing equimolecular quantities of the reactants in methyl alcohol and by the oxidation of the adduct with 50% nitric acid, whereupon 4:6-dinitro-1:3:3-trimethyloxindole (XV) (Beilstein, "Handbuch der Organischen Chemie", 21, 294; Brunner, *Monatsh.*, 1896, 17, 266) was obtained in good yield. Analogues of (XIV; R = Me and *m*-MeO·C₆H₄) have been prepared from trimethylindolenine methiodide with methyl ethynyl ketone and *m*-methoxyphenyl ethynyl ketone, respectively.

A second mol. of phenyl ethynyl ketone could not be added to (XIV) to form an adduct analogous to (III) (*e.g.*, on heating an alcoholic solution in the presence of a small amount of sodium hydroxide or piperidine or on heating in acetic anhydride) and (XIV) was always formed from the condensation of 2:3:3-trimethylindolenine methiodide and phenyl ethynyl ketone, however the ratio of the reactants was varied. The corresponding condensation of the diethylacetal of propionic aldehyde with 2:3:3-trimethylindolenine methiodide gives rise to the indocarbocyanine dyestuff, Astrophloxine FF (XVI), and the intermediate corresponding to (XIV) has not been isolated (Bayer, G.P. 410,487).

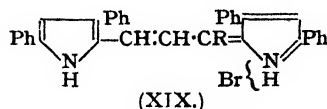
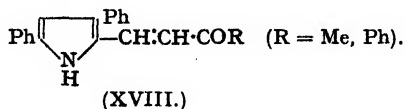


Attempts to condense (XIV; R = Me, Ph) with a second mol. of 2:3:3-trimethylindolenine methiodide have not been successful.

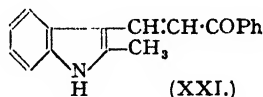
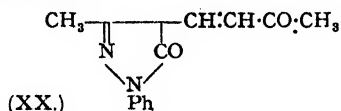
The reaction of 2-methylbenzthiazole ethiodide with *m*-methoxyphenyl ethynyl ketone in the presence of potassium acetate gave a moderate yield of the red adduct (XVII), in which 2 mols. of the ketone had reacted with each mol. of the base, but highly coloured products were not obtained from similar reactions with the ethiodides of 2-methylbenzoxazole or 2-methylbenziminazole. With quinadine and lepidine ethiodides, dark blue adducts were obtained from the

reaction with phenyl ethynyl ketone in methyl-alcoholic solution in the presence of potassium acetate, but the structure of the products has not yet been fully elucidated and will be described in a later paper.

$\alpha\beta$ -Ethyne ketones have also been added to active methylene and methine groups of certain nitrogen heterocyclic compounds. No basic catalyst is required to effect the addition which takes place merely on refluxing the reactants together in methyl-alcoholic solution. With 2 : 4-diphenylpyrrole (Rogers, *J.*, 1943, 590) adducts of the type (XVIII) are readily obtained, the structure of which has been proved by condensation with a further mol. of 2 : 4-diphenylpyrrole in the presence of acids to give the highly coloured salts (XIX) (Cook and Majer, *J.*, 1944, 482).



The reaction of 1-phenyl-3-methyl-5-pyrazolone and methyl ethynyl ketone gave (XX), identical with the product obtained by Gaspar (B.P. 515,998) by the condensation of the pyrazolone with sodio-formylacetone. The addition of phenyl ethynyl ketone to 2-methylindole gave an adduct formulated as (XXI) by analogy with the additions of maleic anhydride (Diels, Alder, and Lübbert, *Annalen*, 1931, 490, 277) and *p*-benzoquinone (Möhlau and Redlich, *Ber.*, 1911, 44, 3605).



EXPERIMENTAL.

(M. p.s are uncorrected, and micro-analyses were carried out by Mr. E. S. Morton.)

4-(3' : 5'-Dibenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine (III).— γ -Picoline (2.8 g.; regenerated from the oxalate) in methyl alcohol (10 c.c.) was added dropwise with stirring to a solution of phenyl ethynyl ketone (8.0 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in methyl alcohol (20 c.c.), the temperature being kept below 30°. The solution became red and then red-violet and the solid adduct was deposited almost immediately. After standing for 3 hours, the solid (10.1 g.) was separated and washed with cold methyl alcohol (20 c.c.). Rapid crystallisation from 2-ethoxyethanol gave 4-(3' : 5'-dibenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine as red-violet needles, m. p. 202–203°. Prolonged boiling of 2-ethoxyethanol solutions caused decomposition, and small quantities of the adduct may be conveniently crystallised from methyl alcohol (Found: C, 81.3; H, 5.4; N, 3.85, 4.05. $\text{C}_{24}\text{H}_{19}\text{O}_2\text{N}$ requires C, 81.6; H, 5.4; N, 4.0%). In order to obtain satisfactory carbon analyses in this series, it was necessary to mix copper oxide with the sample for combustion. Light absorption: maximum 5250 Å., ϵ max. 6920. The adduct formed an orange solution in concentrated sulphuric acid and the red-violet methyl-alcoholic solution of the adduct was turned pink by the addition of dilute acids. The solution was unchanged in colour on addition of 2N-sodium hydroxide or 2N-ammonium hydroxide but turned yellow on addition of 10N-sodium hydroxide solution.

4-(3' : 5'-Dibenzoyl-1'-methylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine (VIII).—4-Ethylpyridine (0.82 g.; Wibaut and Arens, *Rec. Trav. chim.*, 1941, 60, 119) in methyl alcohol (2 c.c.) was added to phenyl ethynyl ketone (2 g.) in methyl alcohol (8 c.c.). The solution rapidly became red-violet and heat was evolved. After standing overnight, the crude solid, m. p. 217–219° (1.6 g.), was separated and crystallised from methyl alcohol (500 c.c.) to yield 4-(3' : 5'-dibenzoyl-1'-methylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine, m. p. 232–233° (Found: C, 81.6; H, 5.7; N, 4.1. $\text{C}_{25}\text{H}_{21}\text{O}_2\text{N}$ requires C, 81.8; H, 5.7; N, 3.8%).

4-(3' : 5'-Di-*m*-methoxybenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine. — γ -Picoline (0.3 g.) in methyl alcohol (1 c.c.) was added to a solution of *m*-methoxyphenyl ethynyl ketone (1.0 g.; Johnson and Melhuish, this vol., p. 346) in methyl alcohol (5 c.c.). The mixture rapidly acquired a red-violet coloration with evolution of heat. After standing overnight, the solid (1.1 g.) was separated, washed with methyl alcohol, and crystallised from 2-ethoxyethanol, 4-(3' : 5'-di-*m*-methoxybenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine being obtained as red-violet needles, m. p. 195–196° [Found: C, 75.1; H, 5.75; OCH_3 , 14.7. $\text{C}_{24}\text{H}_{19}\text{O}_4\text{N}$ requires C, 75.5; H, 5.6; OCH_3 , 15.0%).

4-(3' : 5'-Di-*o*-chlorobenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine. — γ -Picoline (0.3 g.) and *o*-chlorophenyl ethynyl ketone (1.0 g.; see below for preparation) under the conditions of the previous experiment afforded 4-(3' : 5'-di-*o*-chlorobenzoylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine (1.0 g.), which crystallised from 2-ethoxyethanol (5 c.c.) as violet needles, m. p. 140–141° (Found: Cl, 16.9. $\text{C}_{24}\text{H}_{17}\text{O}_2\text{NCl}_2$ requires Cl, 16.8%).

4-(3' : 5'-Diacylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine. — γ -Picoline (0.7 g.) in methyl alcohol (1.0 c.c.) was added to a solution of methyl ethynyl ketone (1.0 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in methyl alcohol (2 c.c.) with external cooling. A vigorous reaction occurred and the solution became reddish-brown. 4-(3' : 5'-Diacylpenta-2' : 4'-dienylidene)-1 : 4-dihydropyridine rapidly

separated and after standing overnight it was collected (1.4 g.) and crystallised from methyl alcohol, forming reddish-brown needles, m. p. 202—203° (Found: C, 73.0; H, 6.75; N, 5.7. $C_{14}H_{11}O_2N$ requires C, 73.35; H, 6.55; N, 6.1%).

o-Chlorophenylethyne carbinol.—Purified acetylene was rapidly passed into liquid ammonia (1000 c.c.) with stirring and cooling, and sodium (23 g.) added in small pieces at such a rate that the blue colour never persisted for more than few moments. A solution of *o*-chlorobenzaldehyde (140 g.; redistilled) in ether (150 c.c.) was added dropwise during 1½ hours, and the mixture was stirred and cooled for a further 3 hours with continued introduction of acetylene. The ammonia was allowed to evaporate overnight and ether and dilute hydrochloric acid (ice) were added to the residue. Isolation of the product in the usual manner gave *o*-chlorophenylethyne carbinol as a pale yellow liquid (73 g.), b. p. 147—148°/26 mm.; n_D^{20} 1.5669 (Found: C, 64.55; H, 4.05. C_8H_7OCl requires C, 64.85; H, 4.2%). In one experiment, *o*-chlorobenzyl alcohol, b. p. 120—125°/18 mm., m. p. 71—72°, formed by a simultaneous Cannizzaro reaction, was isolated from the lower-boiling fractions of the distillation, and it is therefore important not to add the aldehyde too quickly to the sodium acetylide solution.

o-Chlorophenyl Ethynyl Ketone.—To a stirred solution of *o*-chlorophenylethyne carbinol (68 g.) in acetone (80 c.c.), a solution of chromium trioxide (38 g.) in water (120 c.c.) was slowly added in an atmosphere of nitrogen, the temperature of the solution being kept below 15°. After a further hour's stirring, the mixture was poured into water (1000 c.c.) and extracted with ether (3 × 200 c.c.). Evaporation of the ethereal solution gave a yellow solid which recrystallised from petroleum (b. p. 60—80°) to give *o*-chlorophenyl ethynyl ketone (41 g.) as pale yellow needles, m. p. 67—68° (Found: C, 65.45; H, 3.3. C_8H_5OCl requires C, 65.65; H, 3.05%). The ketone readily formed a red insoluble copper derivative and a white insoluble silver derivative.

Phenyl 1-Hexynyl Ketone.—A solution of chromium trioxide (9 g.) in water (28 c.c.) and concentrated sulphuric acid (7.5 c.c.) was added dropwise during 1 hour with stirring to 1-phenyl-2-hexyn-1-ol (18.2 g.; Campbell, Campbell, and McGuire, *Chem. Abs.*, 1941, 35, 5872) in acetone (30 c.c.), the reaction temperature being kept below 15°. The mixture was further stirred for 1 hour at room temperature and then poured into water (300 c.c.), and the product isolated by means of ether. Distillation of the residue after removal of the solvent gave *phenyl 1-hexynyl ketone* as a pale yellow liquid (12.6 g.), b. p. 104°/1 mm.; n_D^{20} 1.5451 (Found: C, 83.5; H, 7.2. $C_{13}H_{14}O$ requires C, 83.85; H, 7.5%).

Oxidation of 4-(3':5'-Dibenzoylpenta-2':4'-dienylidene)-1:4-dihydroxyridine.—The adduct (III) (1.0 g.) was treated with nitric acid (25 c.c.) and water (25 c.c.) and refluxed for 3 hours. Nitrous fumes were evolved and the final solution was clear yellow. After standing overnight, benzoic acid (0.4 g.), m. p. 120—121° after sublimation, was deposited and was separated. The filtrate was concentrated, and on cooling, a further amount of benzoic acid (0.1 g.) was obtained, which was again separated. The filtrate was diluted with water (5 c.c.) and again concentrated, and this process repeated in order to remove the excess of nitric acid. The residue was again diluted with water (5 c.c.) and the filtered solution extracted with ether (3 × 5 c.c.). The aqueous layer was treated with excess of picric acid solution and the first-formed low-melting precipitate removed. After standing overnight, isonicotinic acid picrate separated as stout yellow needles (0.25 g.), m. p. 214—215° after crystallisation from water (Found: C, 40.65; H, 2.45; N, 15.85. $C_{12}H_8O_6N_4$ requires C, 40.6; H, 2.3; N, 15.8%). The m. p. of this derivative was not depressed on admixture with an authentic specimen, prepared from the isonicotinic acid obtained by permanganate oxidation of γ -picoline (Koelsch, *J. Amer. Chem. Soc.*, 1943, 65, 2464). A mixture of isonicotinic acid picrate with nicotinic acid picrate, m. p. 210—211° (Found: C, 40.6; H, 2.7%), had m. p. 186—199°.

1:3:3-Trimethyl-2-(3'-benzoylallylidene)dihydroindole (XIV; R = Ph).—Phenyl ethynyl ketone (4.4 g.) in methyl alcohol (10 c.c.) was added to a solution of 2:3:3-trimethylindolenine methiodide (10 g.) in methyl alcohol (60 c.c.) and the mixture refluxed for 1 minute. A solution of potassium acetate (3.4 g.) in methyl alcohol (6 c.c.) was added to the yellow solution, which rapidly became red. After standing for 3 hours, the precipitated 1:3:3-trimethyl-2-(3'-benzoylallylidene)dihydroindole (9.0 g.; 89%) was separated, and crystallised from methyl alcohol in orange-red prisms, m. p. 158—159° (Found: C, 82.9; H, 7.2; N, 4.95. $C_{21}H_{21}ON$ requires C, 83.15; H, 6.9; N, 4.6%). Light absorption: maximum 4600 Å., ϵ max. 45,100.

1:3:3-Trimethyl-2-pent-2'-en-4'-onylidenedihydroindole (XIV; R = Me).—Methyl ethynyl ketone (0.46 g.) in methyl alcohol (2 c.c.) was added to a solution of 2:3:3-trimethylindolenine methiodide (2 g.) in methyl alcohol (15 c.c.), and the mixture warmed slightly. A solution of potassium acetate (0.34 g.) in methyl alcohol (2 c.c.) was added, and the solution immediately became dark yellow. After standing overnight, the adduct was precipitated by cautious addition of water. 1:3:3-Trimethyl-2-pent-2'-en-4'-onylidenedihydroindole crystallised from 50% aqueous methyl alcohol in long yellow needles, m. p. 130—131° (Found: C, 79.45; H, 7.7; N, 6.05. $C_{18}H_{18}ON$ requires C, 79.65; H, 7.9; N, 5.8%). Light absorption: maximum 4150 Å., ϵ max. 45,800.

1:3:3-Trimethyl-2-(3'-*m*-methoxybenzoylallylidene)dihydroindole (XIV; R = *m*-MeO·C₆H₄).—*m*-Methoxyphenyl ethynyl ketone (1.08 g.) in methyl alcohol (5 c.c.) was added to a solution of 2:3:3-trimethylindolenine methiodide (2 g.) in methyl alcohol (15 c.c.), and the mixture refluxed for 1 minute. A solution of potassium acetate (0.7 g.) in methyl alcohol (5 c.c.) was added, after which the solution acquired a deep red colour and the solid adduct was rapidly deposited. After standing for 3 hours, 1:3:3-trimethyl-2-(3'-*m*-methoxybenzoylallylidene)dihydroindole (2.0 g.) was separated, washed, and crystallised from methyl alcohol (300 c.c.), forming bright red plates, m. p. 182—183° (Found: C, 78.7; H, 6.5; N, 4.85. $C_{22}H_{22}O_2N$ requires C, 78.7; H, 6.5; N, 4.8%). Light absorption: maximum 4600 Å., ϵ max. 46,300.

Oxidation of 1:3:3-Trimethyl-2-(3'-benzoylallylidene)dihydroindole.—The adduct (XIV; R = Ph) (1 g.) was treated with nitric acid (d 1.42; 25 c.c.) and water (25 c.c.) and the mixture refluxed for 3 hours. Nitrous fumes were evolved and the black tar at first produced slowly dissolved and a yellow solution was formed. After cooling, the solution was made alkaline to brilliant-yellow, any solid separated, and the solution extracted with ether (3 × 50 c.c.). Removal of the ether gave a pale brown solid (0.37 g.) which was crystallised from methyl alcohol and then from a small volume of toluene to

gave 4:6-dinitro-1:3:3-trimethyloxindole as pale yellow plates, m. p. 146—147° (Brunner, *loc. cit.*, gives m. p. 148°), alone and mixed with an authentic specimen.

3-Ethyl-2-(3':5'-di-m-methoxybenzoylpenta-2':4'-dienylidene)benzthiazoline (XVII).—*m*-Methoxyphenyl ethynyl ketone (0.52 g.) in methyl alcohol (5 c.c.) was added to a solution of 2-methylbenzthiazole ethiodide (1 g.) in methyl alcohol (5 c.c.), and the mixture warmed slightly. A solution of potassium acetate (0.32 g.) in methyl alcohol (3 c.c.) was added, whereupon the solution became deep red and a solid adduct, m. p. 150—154°, was deposited after standing overnight. The adduct (0.2 g.) was repeatedly crystallised from 2-ethoxyethanol to yield 3-ethyl-2-(3':5'-di-m-methoxybenzoylpenta-2':4'-dienylidene)-benzthiazoline as small red needles, m. p. 171—172° (Found: C, 72.5; H, 5.25; N, 2.9; S, 6.05. $C_{20}H_{22}O_4NS$ requires C, 72.45; H, 5.4; N, 2.8; S, 6.4%).

3:5-Diphenyl-2-(2'-benzoylvinylyl)pyrrole (XVIII; R = Ph).—A solution of 2:4-diphenylpyrrole (1 g.) and phenyl ethynyl ketone (0.6 g.) in methyl alcohol (40 c.c.) was refluxed for one minute and allowed to stand overnight. 3:5-Diphenyl-2-(2'-benzoylvinylyl)pyrrole (1.4 g.) crystallised in orange-red prisms, which were recrystallised from methyl alcohol. The pure adduct, m. p. 212°, dissolved in concentrated sulphuric acid to a red solution (Found: C, 85.9; H, 5.45; N, 3.85. $C_{22}H_{18}ON$ requires C, 85.9; H, 5.45; N, 4.0%).

Bis-2-(3:5-diphenylpyrrole)- α -phenyltrimethincyanine Bromide (XIX; R = Ph).—The foregoing compound (1.75 g.) and 2:4-diphenylpyrrole (1.1 g.) in acetic acid (3 c.c.) were treated with a 50% solution of hydrobromic acid in acetic acid (0.8 c.c.). An immediate deep violet coloration was produced and the mixture was warmed on the steam-bath for 40 minutes. After cooling, the adduct was separated, washed with methyl alcohol, and crystallised from chloroform to give bis-2-(3:5-diphenylpyrrole)- α -phenyltrimethincyanine bromide as violet prisms with a golden lustre, m. p. 245—246° (Cook and Majer, *loc. cit.*, give m. p. 245°).

3:5-Diphenyl-2-(but-1'-en-3'-onyl)pyrrole (XVIII; R = Me).—Prepared similarly to the phenyl analogue from 2:4-diphenylpyrrole (1 g.) and methyl ethynyl ketone (0.3 g.) in methyl alcohol (40 c.c.), and crystallised from methyl alcohol, 3:5-diphenyl-2-(but-1'-en-3'-onyl)pyrrole (1.1 g.) formed orange prisms, m. p. 207°, which dissolved in concentrated sulphuric acid to a deep orange solution (Found: C, 83.3; H, 5.85; N, 5.1. $C_{20}H_{18}ON$ requires C, 83.6; H, 5.9; N, 4.9%).

Bis-2-(3:5-diphenylpyrrole)- α -methyltrimethincyanine Bromide (XIX; R = Me).—The pyrrole (XVIII; R = Me) (0.3 g.) and 2:4-diphenylpyrrole (0.2 g.) in ethyl acetate (2 c.c.) were treated with a 50% solution of hydrobromic acid in acetic acid (0.3 c.c.), and the mixture heated on the steam-bath for one hour. The green dye was separated, and crystallised from ethyl acetate-ether, forming green plates, m. p. 224° (Cook and Majer, *loc. cit.*, give m. p. 225°).

1-Phenyl-3-methyl-4-(but-1'-en-3'-onyl)-5-pyrazolone (XX).—1-Phenyl-3-methyl-5-pyrazolone (1 g.) and methyl ethynyl ketone (0.4 g.) in methyl alcohol (10 c.c.) were refluxed for one minute, and the red solution kept at room temperature for 2 days. 1-Phenyl-3-methyl-4-(but-1'-en-3'-onyl)-5-pyrazolone was separated and crystallised from methyl alcohol, forming yellow hair-like crystals, m. p. 181° (Gaspar, *loc. cit.*, gives m. p. 177°) (Found: C, 69.7; H, 5.3. Calc. for $C_{14}H_{14}O_2N_2$: C, 69.4; H, 5.8%).

2-Methyl-3-(2'-benzoylvinylyl)indole (XXI).—2-Methylindole (1 g.) and phenyl ethynyl ketone (1 g.) were dissolved in methyl alcohol (5 c.c.) and allowed to stand overnight. 2-Methyl-3-(2'-benzoylvinylyl)-indole was separated, and crystallised from methyl alcohol in orange prisms, m. p. 183—184° (Found: C, 82.5; H, 5.6; N, 5.5. $C_{18}H_{14}ON$ requires C, 82.8; H, 5.75; N, 5.35%).

3-Benzoyl-6-phenylpyridine and s-Tribenzoylbenzene.—Phenyl ethynyl ketone (1 g.) in acetic acid (1 c.c.) was treated with a cold saturated solution of ammonium acetate (0.8 g.) in acetic acid, and the mixture kept at room temperature for 3 days. The precipitated solid was thoroughly extracted with 2*N*-hydrochloric acid (3 \times 10 c.c.), and the acid extract basified to Clayton-yellow, whereupon crude 5-benzoyl-2-phenylpyridine was obtained. Repeated crystallisation from alcohol with carbon clarification gave the base as almost colourless plates (0.2 g.), m. p. 86—87° (Bowden and Jones, *J.*, 1946, 953, give m. p. 84—85°). The residue from the acid extract was crystallised from alcohol, and s-tribenzoylbenzene was obtained as colourless needles (0.3 g.), m. p. 119° (Claisen, *Annalen*, 1894, 281, 307, gives m. p. 118—119°).

The author is indebted to Mr. J. D. Rose for his interest in this work.

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[Received, February 8th, 1947.]

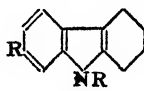
325. *The Friedel-Crafts Reaction with 1-Acyl-2:3-dimethylindoles.*

By W. J. GAUDION, W. H. HOOK, and S. G. P. PLANT.

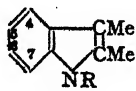
Substances derived from 1-acetyl- and 1-benzoyl-2:3-dimethylindole by the Friedel-Crafts reaction have been hydrolysed to a compound which has been proved to be 6-acetyl-2:3-dimethylindole. 2:3-Dimethyl-6-ethylindole has been obtained from it by reduction and subsequent dehydrogenation, as well as from 2-acetamido-1:4-diethylbenzene by the action of potassium *tert*-butoxide. The results are analogous to those previously observed in the carbazole group. Certain reactions of 1:6-diacetyl-2:3-dimethylindole have been studied.

EARLIER work has shown that while disubstitution at the 3- and 6-positions readily takes place when acid chlorides and anhydrides act under the conditions of a Friedel-Crafts reaction on carbazole and its 9-alkyl derivatives, similar treatment of the 9-acylcarbazoles leads to monosubstitution at the 2-position (see, *e.g.*, Plant, Rogers, and Williams, *J.*, 1935, 741;

Mitchell and Plant, *J.*, 1936, 1295). Plant and Rogers (*J.*, 1936, 40) found that 9-acetyl- and 9-benzoyl-tetrahydrocarbazole gave their 7-acetyl and 7-benzoyl derivatives (I; R = Ac or Bz) under similar conditions, and it seemed probable that the 6-position would be that normally



(I.)



(II.)

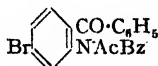


(III.)

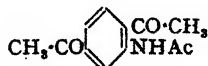
taken by the substituent in Friedel-Crafts reactions with simple indoles such as the 1-acyl-2:3-dimethylindoles (II; R = Acyl). In order to investigate this, 1-acetyl-2:3-dimethylindole was treated with acetyl bromide (or chloride) and aluminium chloride, and a diacetyl-2:3-dimethylindole, m. p. 116°, was obtained. A small quantity of a triacetyl-2:3-dimethylindole was formed at the same time, and this was also prepared by a further application of the Friedel-Crafts reaction to the diacetyl compound, m. p. 116°. 1-Benzoyl-2:3-dimethylindole was converted under similar conditions into an acetyl derivative, which, on hydrolysis, gave an acetyl-2:3-dimethylindole, m. p. 154°, identical with that obtained by the hydrolysis of the diacetyl compound. That the substance, m. p. 154°, was not 5-acetyl-2:3-dimethylindole was proved by reducing it by the Clemmensen method. The resulting 2:3-dimethylethylindoline, which formed a characteristic phenylcarbamyl derivative, gave, on dehydrogenation, a 2:3-dimethylethylindole, m. p. 74°, different from 2:3-dimethyl-5-ethylindole synthesised from *p*-ethylphenylhydrazine and methyl ethyl ketone. Further investigations into the structure of these products had to be discontinued early in 1940 for the duration of the war. In the meantime Borsche and Groth (*Annalen*, 1941, 549, 238) have treated 1-acetyl-2:3-dimethylindole with acetyl chloride and aluminium chloride and obtained a compound, m. p. 115–116°, which they called 1:6-diacetyl-2:3-dimethylindole. It was hydrolysed to a substance, m. p. 153°, stated to be 6-acetyl-2:3-dimethylindole. No experimental evidence was adduced for the structures, which were assigned on the basis of the work of Plant and others referred to above.

The validity of these assumptions has now been established by the synthesis of 2:3-dimethyl-6-ethylindole from 2-acetamido-1:4-diethylbenzene (III), m. p. 154°, by heating it with potassium *tert*-butoxide under conditions similar to those used by Marion and Ashford (*Canadian J. Res.*, 1945, 23B, 26; see also Tyson, *J. Amer. Chem. Soc.*, 1941, 63, 2024) for the preparation of 2:3-dimethylindole from *o*-acetamidoethylbenzene. The product proved to be identical with the substance, m. p. 74°, obtained by the reactions already mentioned. Voswinkel (*Ber.*, 1889, 22, 315) claims to have prepared 2-acetamido-1:4-diethylbenzene from the corresponding amine, obtained from 2-nitro-1:4-diethylbenzene, but the m. p. is given as 99° and the substance was not analysed. The conditions described in the experimental section for the nitration of *p*-diethylbenzene were found to be more satisfactory than those mentioned by Voswinkel, which led to a considerable quantity of a dinitro-compound, as was evident from the fact that a bisacetamido-1:4-diethylbenzene could be prepared from the basic material obtained by reduction of the product.

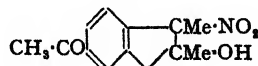
Koelsch (*J. Amer. Chem. Soc.*, 1944, 66, 1983) has found that 6-bromo-1-acetyl-2:3-dimethylindole can be oxidised to 5-bromo-2-benzoyl-*N*-acetylbenzanilide (IV) by chromic acid in acetic acid solution. When 1:6-diacetyl-2:3-dimethylindole was treated in this way,



(IV.)



(V.)



(VI.)

2:5-diacetylacetanilide (V) was isolated, evidently after removal of one of the *N*-acetyl groups from the analogous primary oxidation product. It was also found that *o*-acetamidoacetophenone could be similarly obtained from 1-acetyl-2:3-dimethylindole. Nitration of 1:6-diacetyl-2:3-dimethylindole has given a nitro-derivative together with 3-nitro-2-hydroxy-1:6-diacetyl-2:3-dimethylindoline (VI). The latter, which was colourless, soluble in alkali, and melted with evolution of oxides of nitrogen, had the behaviour characteristic of this type of compound, the formation of which is a well-established feature of the 1-acyl-2:3-dialkylindoles (see, *e.g.*, *J.*, 1933, 955; 1940, 283).

3-Acetylcarbazole can be readily prepared by heating 9-acetylcarbazole with aluminium chloride in nitrobenzene (Plant, Rogers, and Williams, *loc. cit.*). Attempts to obtain 5-acetyl-2:3-dimethylindole similarly from the 1-acetyl compound have given an unsatisfactory

product, from which a little 6-acetyl-2:3-dimethylindole was the only pure material isolated. This behaviour is reminiscent of that observed with 9-acetyltetrahydrocarbazole (Plant and Rogers, *loc. cit.*).

EXPERIMENTAL.

1:6-Diacetyl-2:3-dimethylindole.—Aluminium chloride (25 g.) was added to 1-acetyl-2:3-dimethylindole (9.4 g.) and acetyl bromide (17 g.) in carbon disulphide (120 c.c.), the whole refluxed for 2½ hours, the solvent distilled off, and the residue added to ice-dilute hydrochloric acid. When the product was crystallised from alcohol, 1:6-diacetyl-2:3-dimethylindole (8.5 g.) was obtained in colourless prisms, m. p. 116° (Found: C, 73.2; H, 6.5. Calc. for $C_{14}H_{12}O_2N$: C, 73.4; H, 6.5%). The same substance resulted from the use of a restricted amount (6.4 g.) of acetyl chloride instead of acetyl bromide. When the material obtained by concentrating the alcoholic mother liquors was recrystallised from light petroleum, a triacetyl-2:3-dimethylindole separated in colourless needles, m. p. 117° (Found: C, 76.8; H, 6.3. $C_{14}H_{10}O_3N$ requires C, 76.8; H, 6.3%).

The same triacetyl compound (mixed m. p.) was obtained in good yield when a mixture of 1:6-diacetyl-2:3-dimethylindole (1.15 g.), acetyl chloride (0.5 g.), aluminium chloride (2.5 g.), and carbon disulphide (15 c.c.) was refluxed for 2 hours, and the product crystallised from alcohol.

1-Benzoyl-6-acetyl-2:3-dimethylindole.—When 1-benzoyl-2:3-dimethylindole (5 g.) was treated with acetyl chloride (2.4 g.) and aluminium chloride (8 g.) in carbon disulphide (50 c.c.) as described for the corresponding acetyl compound, and the product crystallised from alcohol, 1-benzoyl-6-acetyl-2:3-dimethylindole was obtained in colourless needles (4 g.), m. p. 117° (Found: C, 78.0; H, 5.9. $C_{15}H_{12}O_2N$ requires C, 78.3; H, 5.8%). After its solution in aqueous-alcoholic potassium hydroxide had been refluxed for 2 hours, the addition of water precipitated 6-acetyl-2:3-dimethylindole. This separated from aqueous alcohol in yellow prisms, m. p. 154° (Found: N, 7.3. Calc. for $C_{13}H_{10}ON$: N, 7.5%), identical (mixed m. p.) with the substance similarly obtained from 1:6-diacetyl-2:3-dimethylindole.

2:3-Dimethyl-6-ethylindole.—After *p*-ethylphenylhydrazine (2.89 g.) and methyl ethyl ketone (1.54 g.) had been warmed for a few minutes on the steam-bath, the resulting hydrazone was taken up in ether, the solution dried (K_2CO_3), and evaporated. The residue was heated with powdered zinc chloride (2 g.) at 180° for 5 minutes, and the product extracted with boiling light petroleum. 2:3-Dimethyl-6-ethylindole separated from the extract in colourless plates, m. p. 62° (Found: C, 82.9; H, 8.9. $C_{12}H_{15}N$ requires C, 83.2; H, 8.7%).

2:3-Dimethyl-6-ethylindole.—(a) 6-Acetyl-2:3-dimethylindole (4.7 g.) and concentrated hydrochloric acid (30 c.c.) were added to amalgamated granulated zinc (50 g.), the mixture shaken, and left overnight. After the addition of more hydrochloric acid (100 c.c. of 28%), the whole was refluxed for 12 hours, made alkaline with concentrated aqueous sodium hydroxide, and steam distilled. When the distillate was extracted with ether, and the extract dried and fractionated, 2:3-dimethyl-6-ethylindole (2.2 g.) was obtained as a colourless oil, b. p. 133°/13 mm. (Found: C, 82.7; H, 10.4. $C_{12}H_{15}N$ requires C, 82.3; H, 9.7%). The base (1 g.) was heated with palladised charcoal (0.25 g.) for 4 hours at 260° in an atmosphere of hydrogen, the product dissolved in acetone, the solution filtered and poured into dilute hydrochloric acid. The precipitated solid was crystallised from aqueous alcohol, from which 2:3-dimethyl-6-ethylindole separated in colourless plates, m. p. 74°, which soon turned brown when left in air (Found: C, 82.7; H, 8.6%).

(b) *p*-Diethylbenzene (20 g.) was gradually added to a well stirred mixture of glacial acetic acid (40 c.c.) and nitric acid (43 c.c., *d* 1.5) at 10–15°, the whole diluted with water, and the product extracted with chloroform. After the extract had been washed with aqueous sodium carbonate, dried, and the solvent removed, 2-nitro-1:4-diethylbenzene (17.4 g.) was obtained, on distillation, as a yellow oil, b. p. 137–140°/12 mm. with some decomposition. The oil (16.5 g.) was heated on the steam-bath for an hour with iron filings (65 g.) and aqueous acetic acid (70 c.c. of 5%), the mixture made alkaline with aqueous sodium carbonate, and the base removed in steam. When extracted from the distillate with ether, dried, and distilled, 2-amino-1:4-diethylbenzene (12.5 g.) was obtained as a colourless oil, b. p. 122°/13 mm. The amine was suspended in three times its volume of water, treated with a slight excess of acetic anhydride, the mixture boiled, and sufficient glacial acetic acid added to effect solution. On cooling, 2-acetamido-1:4-diethylbenzene separated in good yield in colourless needles, m. p. 154° (Found: C, 75.3; H, 8.8; N, 7.5. $C_{14}H_{17}ON$ requires C, 75.4; H, 8.9; N, 7.3%). The acetyl compound (3 g.) was added to a solution of potassium (0.91 g.) in *tert*-butyl alcohol (19 g.), the excess of the alcohol distilled off, and the residue heated at 350–360° for 20 minutes in an atmosphere of nitrogen. When cold, the mixture was treated with water, and the 2:3-dimethyl-6-ethylindole removed in steam. It then separated from aqueous alcohol in colourless plates, m. p. 74°, identical (mixed m. p.) with the substance described above.

After *p*-diethylbenzene (10 g.) had been nitrated by adding it to nitric acid (20 c.c., *d* 1.5) at 0° as described by Voswinkel (*loc. cit.*), and the crude product, without distillation, reduced as described above, the 2-amino-1:4-diethylbenzene was removed in steam and the residual hot aqueous solution filtered. The solid was washed several times with hot water and the united filtrates saturated with salt and extracted with benzene. The extract was dried, acetic anhydride (10 c.c.) added, and the whole refluxed for a few minutes. When cold, the bulky precipitate was collected and recrystallised from cyclohexanone, from which a bisacetamido-1:4-diethylbenzene (2.2 g.) was obtained in pale yellow prisms, m. p. 253–256° (Found: C, 67.6; H, 7.9; N, 11.4. $C_{14}H_{19}O_2N_2$ requires C, 67.7; H, 8.1; N, 11.3%).

1-Phenylcarbonyl-2:3-dimethyl-6-ethylindole.—After a mixture of the indoline with a little less than one molecular proportion of phenyl isocyanate had been heated on the steam-bath for a few minutes, the solid was crystallised from alcohol, and 1-phenylcarbonyl-2:3-dimethyl-6-ethylindole obtained in colourless needles, m. p. 218° (Found: C, 77.1; H, 7.5; N, 9.5. $C_{18}H_{17}ON_2$ requires C, 77.5; H, 7.5; N, 9.5%).

2:5-Diacetylacetanilide.—Chromic anhydride (2.7 g.) in a little water was added to a solution of 1:6-diacetyl-2:3-dimethylindole (3.8 g.) in glacial acetic acid (80 c.c.), the whole left for 2 hours at

room temperature, and then heated for 5 minutes at 70°. After the addition of water (300 c.c.), the filtered solution was extracted with benzene, and the extract shaken with aqueous sodium carbonate, dried (MgSO₄), and evaporated under reduced pressure. When the residue was crystallised from alcohol, 2:6-diacylacetanilide (1.45 g.) was obtained in yellow needles, m. p. 103° (Found: C, 65.9; H, 5.2; N, 6.4. C₁₁H₁₀O₃N requires C, 65.8; H, 5.9; N, 6.4%).

After 1-acetyl-2:3-dimethylindole (3.7 g.) had been similarly oxidised and the product twice crystallised from water, o-acetamidoacetophenone was obtained in pale yellow needles (1.25 g.), m. p. 75° (Found: C, 67.7; H, 6.1; N, 8.3. Calc. for C₁₀H₁₁O₃N: C, 67.8; H, 6.2; N, 7.9%).

Nitration of 1:6-Diacetyl-2:3-dimethylindole.—Nitric acid (0.3 c.c., d 1.5) was added dropwise to a solution of 1:6-diacetyl-2:3-dimethylindole (1 g.) in glacial acetic acid (3 c.c.) at 80°. On cooling, a nitro-derivative (0.2 g.) slowly separated, and, after recrystallisation from acetic acid, it was obtained in practically colourless needles, m. p. 185° (Found: C, 60.9; H, 5.0; N, 10.6. C₁₄H₁₄O₄N₂ requires C, 61.3; H, 5.1; N, 10.2%). When the mother liquor was concentrated under reduced pressure, a small amount of 3-nitro-2-hydroxy-1:6-diacetyl-2:3-dimethylindoline separated. On recrystallisation from acetic acid it was isolated in colourless prisms, m. p. 125° (decomp.) (Found: N, 9.8. C₁₄H₁₄O₄N₂ requires N, 9.6%).

Action of Aluminium Chloride on 1-Acetyl-2:3-dimethylindole.—After a solution of the acetyl compound (2 g.) and aluminium chloride (2 g.) in nitrobenzene (20 c.c.) had been heated at 115° for 20 minutes, water was added, and the nitrobenzene removed in steam. When the residual sticky solid was dried, distilled under reduced pressure, and twice recrystallised from alcohol, a small amount of 6-acetyl-2:3-dimethylindole was obtained in yellow prisms, m. p. 151–153°, and identified by mixed m. p.

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[Received, February 10th, 1947.]

326. *The Stereochemistry of Organic Derivatives of Phosphorus. Part II. The Synthesis of 2:2-Disubstituted 1:2:3:4-Tetrahydroisophospholinium Salts and the Optical Resolution of 2-Phenyl-2-p-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium Bromide.*

By FREDERICK G. HOLLIMAN and FREDERICK G. MANN.

Numerous attempts to synthesise the tetrahydroisophospholine ring system by the use of o-2-bromoethylbenzyl bromide (cf. Holliman and Mann, *J.*, 1942, 737; 1943, 547, 550) and by other methods having failed, a general synthesis for 2:2-diaryl-1:2:3:4-tetrahydroisophospholinium salts has been developed and applied to the preparation of 2-phenyl-2-p-bromophenyl- and 2-phenyl-2-p-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium bromides. Whilst the former salt resisted all attempts at resolution into optically active forms, the dextrorotatory form of the latter, having $[M]_D + 32.9^\circ$, was isolated on one occasion: the corresponding levorotatory form could not be obtained nor could the successful resolution be repeated, these failures being attributed to the formation of partial racemates. This represents the first recorded example of an asymmetric quaternary phosphonium salt showing optical activity.

THE ready resolution of 2-phenyl-2-p-chlorophenacyl-1:2:3:4-tetrahydroisarsinolinium bromide (I) and the high optical stability of the isomers obtained (Holliman and Mann, *J.*, 1943, 550), in contrast to the fleeting rotation displayed by other optically active arsonium salts (Burrows and Turner, *J.*, 1921, 19, 426; Kamai, *Ber.*, 1933, 66, 1779; *J. Gen. Chem. Russia*, 1934, 4, 184), was attributed to the great chemical stability of the above heterocyclic ring system and the consequent inability for racemisation to proceed by a dissociation equilibrium:



It was pointed out that such an equilibrium was almost certainly responsible for the many previous unsuccessful attempts to resolve quaternary arsonium salts, particularly since these salts always contained at least one alkyl group which would lend itself very readily to the above dissociation.

It would seem that similar arguments could be put forward to explain the lack of success attending some of the many attempts to resolve quaternary phosphonium salts [e.g., Pope and Gibson (*J.*, 1912, 101, 735) failed to resolve phenyl-p-tolylbenzylmethylphosphonium iodide, Wedekind (*Ber.*, 1912, 45, 2933) failed with phenyl-p-tolylmethylethylphosphonium iodide, and Meisenheimer *et al.* (*Annalen*, 1926, 449, 213) had no success with phenylbenzylmethylethylphosphonium iodide] but in the majority of cases, investigators have been handicapped by the inherent difficulties involved in the crystallisation of phosphonium salts with optically active anions (Michaelis, *Annalen*, 1901, 315, 43; Pope and Gibson, *loc. cit.*; Wedekind, *loc. cit.*; Radcliffe and Brindley, *J. Soc. Chem. Ind.*, 1923, 42, 64; Kamai, *J. Gen.*

Chem. Russia, 1932, 2, 526; Davies and Mann, *J.*, 1944, 276). On the other hand, evidence has been produced that phosphonium salts do not undergo dissociation in solution as postulated above (Wedekind, *loc. cit.*, but cf. Davies and Lewis, *J.*, 1934, 1600) and it may be that when crystalline salts have been obtained, they have been in the form of partial racemates: if such a form is less soluble than either of the two diastereoisomerides, resolution is obviously impossible.

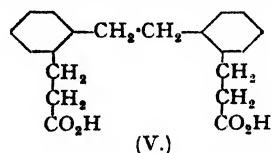
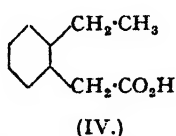
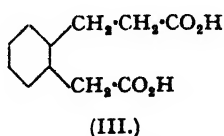
As a sequel to the successful resolution of the asymmetric arsonium salt (I) it seemed highly probable that, could the analogous phosphorus compound, 2-phenyl-2-*p*-chlorophenacyl-1:2:3:4-tetrahydroisophospholinium bromide (II), be prepared it would be possible to



resolve it into optically active forms: crystallisation difficulties would be overcome since derivatives of (II) would probably be isomorphous with corresponding derivatives of (I), and in addition a dissociation equilibrium would be unlikely to operate.

The application of similar methods for the synthesis of (II) to those employed for the arsenic analogue (I) gave only poor yields in the first stage (*i.e.*, the Michaelis reaction between *o*-2-bromoethylbenzyl bromide, phenyldichlorophosphine and sodium in an ethereal medium with ethyl acetate as a catalyst to give 2-phenyl-1:2:3:4-tetrahydroisophospholine) as has already been reported (Holliman and Mann, *J.*, 1943, 548) and subsequent attempts to improve the yields by varying the solvent, the proportions of the reactants, and the catalyst all met with no success. The reasons for this failure are not difficult to formulate. The Michaelis reaction is known to proceed much more slowly in the case of phosphorus halides than with those of arsenic: for example, bromobenzene, phosphorus trichloride, and sodium in ether require 48 hours' refluxing to obtain a small yield of triphenylphosphine (Michaelis and Gleichman, *Ber.*, 1882, 15, 801) whilst the analogous reaction with arsenic trichloride proceeds vigorously and is complete in a short time to give high yields of triphenylarsine (Michaelis and Reese, *ibid.*, p. 2876). On the other hand, the rate of quaternary phosphonium salt formation by the interaction of tertiary phosphines with alkyl halides is many times more rapid than the similar formation of quaternary arsonium salts: the reaction between phenyldiethylphosphine and ethyl iodide in acetone is more than 90% complete after 60 hours, whilst the corresponding reaction with the arsenic analogue is only 20% complete in the same time (Davies and Lewis, *loc. cit.*). Hence, as fast as the phenylisophospholine is formed, phosphonium salt formation takes place with the unreacted *o*-2-bromoethylbenzyl bromide. In another investigation, it was apparent that *p*-tolylidichloroarsine took part in the Michaelis reaction with greater ease than did phenyldichloroarsine. Consequently, the reaction of *p*-tolylidichlorophosphine with *o*-2-bromoethylbenzyl bromide and sodium was investigated in the hope that the rate of phosphine formation would be markedly increased relative to the rate of subsequent phosphonium salt formation, and that a possibly small but workable yield of 2-*p*-tolyl-1:2:3:4-tetrahydroisophospholine would result. This, however, proved not to be the case, only a small amount of distillate being obtained. The latter did in fact appear to be the required tertiary phosphine since it reacted in benzene solution with *p*-chlorophenacyl bromide to give the crystalline 2-*p*-tolyl-2-*p*-chlorophenacyl-1:2:3:4-tetrahydroisophospholinium bromide (as II), but the yield was too small to justify prolonged experimental work to accumulate sufficient of the phosphonium salt for resolution purposes.

Attention was now directed to a fuller investigation of the conditions under which *o*-2-bromoethylbenzyl bromide would react with magnesium with a view to the use of the di-Grignard reagent from the dibromide for the synthesis of tetrahydroisophosphinolines. Employing the entrainment method, *i.e.*, admixture of the dibromide with ethyl bromide, it was found that reaction with magnesium would take place. Treatment of the reagent so produced

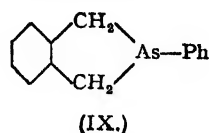
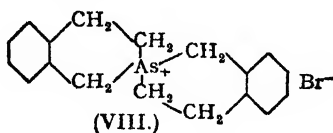
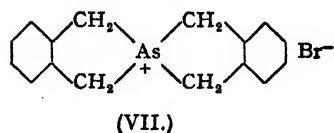


with carbon dioxide was used as a diagnostic method for the presence of the required Grignard reagent, it being anticipated that β -*o*-carboxymethylphenylpropionic acid (III) would be

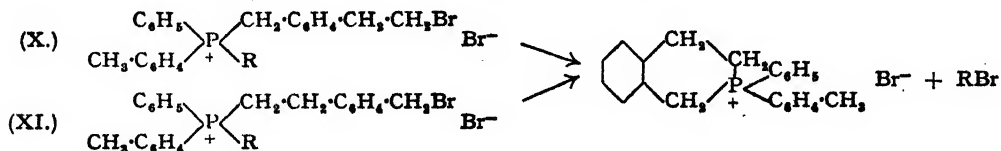
obtained. However, the alkali-soluble fraction of the reaction product was a mixture from which were isolated *o*-ethylphenylacetic acid (IV) and a compound, $C_{20}H_{22}O_4$, which was probably either (V) or an isomer thereof. The isolation of these two acids would indicate that the di-Grignard reagent had, in fact, been produced; it then underwent coupling reactions and subsequent reaction with carbon dioxide to give acids of the type (V), or only partly reacted with carbon dioxide to give (IV). Obviously, it is only the yield of (III) and (IV) which is the measure of the degree to which this type of reaction could be employed in the synthesis of tetrahydroisophosphinolines, and the low yield actually obtained caused this method to be abandoned in favour of other syntheses, which, at the time, showed greater promise of success.

The impracticability of synthesising the phenylisophosphinoline necessary for the preparation of the phosphorus analogue of our arsonium salt led us to consider possible routes for the synthesis of a somewhat different type of phosphinolinium salt. The stability of this type of heterocyclic system has already been discussed and it has been pointed out (Davies and Mann, *loc. cit.*) that a quaternary phosphonium salt with four *aryl* groups attached to the phosphorus atom would not be susceptible to a dissociation equilibrium of the type postulated above. A 2:2-diaryl-1:2:3:4-tetrahydroisophospholinium salt of type (VI) would combine both these features and would probably be resolvable provided difficulties of crystallisation could be overcome: it was of course realised that such a pronounced change in constitution from that of our arsonolinium salt would no longer offer the possibility of isomorphism, and the absence of the *p*-chlorophenacyl group, to which we have ascribed the high rotation characteristic of that salt and similar salts with sulphur, selenium, or tellurium as the hetero-atom (Holliman and Mann, *J.*, 1945, 37), might lead to a very pronounced decrease in any optical activity which might be observed.

The pyrolysis of quaternary arsonium salts carrying a methyl group leads to the elimination of that group as methyl halide and the formation of a tertiary arsine. With quaternary arsonium salts of a suitable type this reaction may be employed for the synthesis of heterocyclic systems. For example, Lyon and Mann (*J.*, 1945, 30) have used this reaction for the preparation of *As*-spiro-bisisoarsindolinium bromide (VII), Holliman and Mann (*J.*, 1945, 45) have analogously prepared the spirocyclic arsonium salt (VIII), and Lyon, Mann, and Cookson (this vol., p. 662) have synthesised the simpler heterocyclic system of 2-phenylisoarsindoline (IX).



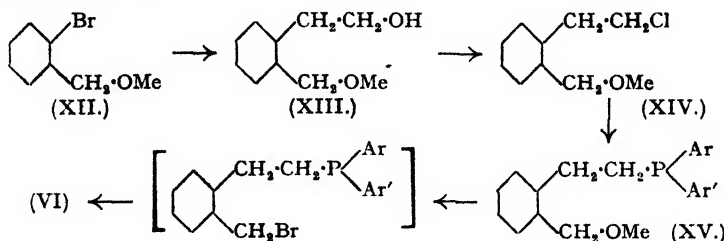
The application of this method to the synthesis of 2:2-diaryl-1:2:3:4-tetrahydroisophospholinium salts was therefore investigated. Meisenheimer *et al.* (*loc. cit.*) have shown that the ease with which radicals are split from quaternary phosphonium chlorides is in the order $Et > CH_3Ph > Me > Pr > isoamyl > Ph$. Accordingly, phenyl-*p*-tolylethylphosphine was brought into reaction with an equimolecular proportion of *o*-2-bromoethylbenzyl bromide to give a crystalline, homogeneous quaternary phosphonium salt which was almost certainly phenyl-*p*-tolyl-*o*-(2-bromoethyl)benzylethylphosphonium bromide (X, $R = Et$) and not the isomeric



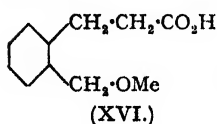
salt (XI, $R = Et$). However, when this salt was heated under varying conditions, although extensive decomposition took place, none of the desired cyclised product could be isolated and examination of the volatile products evolved during the decomposition failed to show any ethyl bromide. Similar experiments involving the use of the corresponding methyl compounds (X or XI; $R = Me$) also proved fruitless.

It was felt that the readiness with which tertiary phosphines form quaternary salts with alkyl halides could be advantageously employed for closing the tetrahydroisophosphinoline

ring, and ultimately the following general synthesis of 2:2-diaryl-tetrahydroisophospholinium salts was successfully developed.



The compounds (XII) and (XIII) are, of course, analogous to intermediates in the synthesis of *o*-2-bromoethylbenzyl bromide and were prepared by similar methods: *o*-bromobenzyl bromide when treated with a methyl-alcoholic solution of sodium methoxide gave *o*-bromobenzyl methyl ether (XII) which was in turn converted into the Grignard reagent by the entrainment method and then treated with ethylene oxide to give *o*-2-hydroxyethylbenzyl methyl ether (XIII). Replacement of the hydroxyl group of the alcohol (XIII) was first attempted using phosphorus tribromide, but fission of the ether grouping also occurred and *o*-2-bromoethylbenzyl bromide together with isochroman were the main products of the reaction; by the use of the theoretical quantity of thionyl chloride in the presence of one molecular proportion of pyridine good yields of *o*-2-chloroethylbenzyl methyl ether (XIV) were obtained. Conversion of the chloro-compound into the Grignard reagent followed by treatment with a diarylchlorophosphine then gave the



tertiary phosphine (XV). At first, difficulty was experienced in the formation of the Grignard reagent from (XIV), and again the carbon dioxide method was employed so that the yields of β -*o*-methoxymethylphenyl-propionic acid (XVI) isolated gave an indication of the yields of the Grignard reagent under various conditions. By far the best reproducible yields were obtained by running a mixture of the chloro-compound with

$\frac{1}{2}$ mol. of ethyl bromide in ethereal solution on to ordinary magnesium turnings, although the chloro-compound alone would react with activated magnesium.

When the tertiary phosphine (XV) was heated in a mixture of constant-boiling hydrobromic acid and glacial acetic acid, the three stages, *i.e.*, cleavage of the ether grouping, esterification, and ring closure, necessary to complete the synthesis were accomplished in one operation, giving good yields of the isophospholinium salt (VI): a stream of hydrogen bromide mixed with hydrogen was passed through the solution in order that the hydrogen bromide concentration should be maintained and that the methyl bromide produced in the ether cleavage should be removed as fast as it was formed, thus being prevented from reacting with the tertiary phosphine.

The above synthesis was first employed to prepare 2-phenyl-2-*p*-bromophenyl-1:2:3:4-tetrahydroisophospholinium bromide (VI; Ar = Ph, Ar' = *p*-C₆H₄Br) as a crystalline solid which with an aqueous solution of sodium picrate gave the phospholinium picrate. The intermediate phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine (XV; Ar = Ph, Ar' = *p*-C₆H₄Br) was obtained as a colourless, viscous, high-boiling liquid which readily reacted with methyl iodide in ethereal solution to give the crystalline methiodide.

For resolution, the bromide was converted by the usual method into the *d*-bromocamphorsulphonate, the *d*-hydrogen tartrate and the *l*-*N*-1-phenylethylphthalamate,* but all these salts were non-crystalline glasses or syrups: the *d*-camphorsulphonate was obtained crystalline but repeated recrystallisation from alcoholic ether failed to produce any evidence that a mixture of diastereoisomerides was present.

The introduction of a hydroxyl group into one of the two aryl groups was considered to be a likely means of increasing the probability that crystalline phosphonium salts with optically active anions would be obtained: should these derivatives not prove suitable, benzylation of the hydroxyl group or some similar procedure might again increase the crystallisability. Accordingly, employing phenyl-*p*-anisylchlorophosphine in place of the phenyl-*p*-bromophenyl-chlorophosphine previously used, we were able to prepare phenyl-*p*-anisyl-2-(*o*-methoxymethylphenyl)ethylphosphine (XV; Ar = Ph, Ar' = *p*-C₆H₄OMe), again characterised by the formation of the methiodide. The demethylation-ring closure procedure also resulted in the demethylation

* For the preparation of the phthamic acid and its conversion into the silver salt, see Mann and Watson, this vol., p. 510.

of the *p*-anisyl group and the crystalline 2-phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophosphinolinium bromide (VI; Ar = Ph, Ar' = *p*-C₆H₄·OH) was thus readily obtained in high yield. That this product did in fact contain a free hydroxyl group was shown by its conversion into the *acetyl* derivative.

The effect of the introduction of the hydroxyl group was soon apparent, as the *d*-bromocamphorsulphonate prepared from the bromide was readily obtained in the crystalline state. Again, however, repeated recrystallisation from a variety of solvents failed to produce any indication that resolution was proceeding.

Similarly, the *d*-camphorsulphonate, originally obtained as a glass, readily crystallised from an acetone solution, and then had m. p. 153—158° and $[M]_D + 102^\circ$ in alcoholic solution. Slow recrystallisation from ethyl acetate—ethyl alcohol gave a first crop having m. p. 171—172.5° and $[M]_D + 110^\circ$, whilst a second and a third crop had respectively, m. p. 153—157° and 142—151°, $[M]_D + 104^\circ$ and $+ 98.4^\circ$. That the first crop was virtually the optically pure *d*-phosphonium *d*-camphorsulphonate was evident since three more recrystallisations of this crop raised the m. p. to a constant value of 174—175° and the $[M]_D$ to $+ 113.5^\circ$.

An alcoholic solution of the optically pure camphorsulphonate, treated at 0° with an alcoholic solution of calcium bromide, furnished the *d*-phosphinolinium bromide, m. p. 268—270°, with $[M]_D + 32.9^\circ$ in aqueous alcoholic solution: it is noteworthy that the *dl*-phosphinolinium bromide had m. p. 287—287.5° and that the optically active salt was considerably more soluble than the racemic compound. A curious solvent effect was observed in methyl alcohol, solutions of the bromide in this solvent having very low activity: this was not due to racemisation, for the bromide recovered from such solutions had the normal activity when again dissolved in aqueous ethyl alcohol. The optical stability and purity of the active bromide is shown by the fact that recrystallisation from boiling ethyl alcohol failed to affect the rotatory power.

The following values for the rotatory dispersion in the visible spectrum were obtained for a 1.029% solution of the *d*-bromide in aqueous-alcoholic solution. The calculated rotations are obtained from the equation $\alpha = k/(\lambda^2 - \lambda_0^2)$, where $k = 0.0885$ and $\lambda_0^2 = 0.0948$, $\lambda_0 = 3078 \text{ \AA}$.

Source of light.	Li.	Na.	Hg.	Hg.	Cu.	Zn.	Hg.
$\lambda, \text{ \AA}.$	6104	5893	5780	5461	5219	4810.5	4358
$\alpha, \text{ obs.}$	$+0.31^\circ$	0.36°	0.37°	0.435°	0.48°	0.64°	0.93°
$[M]_D$	$+30.05^\circ$	34.9°	35.9°	42.2°	46.5°	62.0°	90.1°
$\alpha, \text{ calc.}$	$+0.32^\circ$	0.35°	0.37°	0.435°	0.50°	0.65°	0.93°
$\alpha, \text{ obs.} - \alpha, \text{ calc.}$	-0.01°	$+0.01^\circ$	0.00°	0.00°	-0.02°	-0.01°	0.00°

The close agreement between the observed and the calculated values indicates that the bromide probably possesses simple dispersion, although readings for a much greater number of wave-lengths would have to be obtained to establish this beyond doubt.

In order to obtain the *l*-bromide, the phosphinolinium bromide was recovered from the second and third fractions of the *d*-camphorsulphonate and then converted into the *l*-camphorsulphonate. This salt, like its isomer, was initially obtained as a glass which was crystallised from an acetone solution and then had m. p. 152—157°. When recrystallisation of this salt from ethyl acetate—ethyl alcohol was attempted, the hot solution rapidly began to deposit crystalline material and a much greater proportion of alcohol than was used in the case of the *d*-camphorsulphonate had to be employed before solution was again obtained. In this case, on cooling, practically the whole of the salt was recovered with m. p. 170—172° and $[M]_D - 102^\circ$: further recrystallisation failed to change either the m. p. or the rotatory power. The salt was much less soluble than had been anticipated for the *l*-phosphinolinium *l*-camphorsulphonate and conversion into the phosphinolinium bromide gave only an optically inactive product, m. p. 286—288°: it therefore became apparent that the *l*-camphorsulphonate was now crystallising as a partial racemate. Numerous attempts to re-obtain the low-melting form were of no avail: the less soluble, high-melting form was always obtained in the presence of nuclei, whilst, if steps were taken to ensure that nuclei were excluded, solutions remained supersaturated indefinitely. Similarly, further preparations of the *d*-camphorsulphonate always gave a product, m. p. 170—172°, which, by treatment with calcium bromide, furnished the optically inactive bromide. Attempts to extend the resolution were therefore abandoned.

It is noteworthy that the above 2-phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophosphinolinium bromide is the first quaternary phosphonium salt to be resolved into optically active forms. The only other types of organic phosphorus derivatives (*i.e.*, derivatives containing C—P links) to be obtained in optically active forms are the tertiary phosphine oxides, such as phenylbenzylmethylphosphine oxide, resolved by Meisenheimer *et al.* (*Ber.*, 1911, 44,

356; *Annalen*, 1926, **440**, 224), and the tertiary phosphine sulphide, phenyl-*p*-carboxymethoxyphenyl-*n*-butylphosphine sulphide, resolved by Davies and Mann (*loc. cit.*).

EXPERIMENTAL.

(All rotations were taken by use of a 4-dm. tube. M. p.s are uncorrected.)

2-*p*-Tolyl-2-*p*-chlorophenacyl-1:2:3:4-tetrahydroisophospholinium Bromide (as II).—*o*-2-Bromoethylbenzyl bromide (29 g.) and *p*-tolylidichlorophosphine (19.3 g., 1 mol.) in absolute ether (350 c.c.) were treated with sodium wire (18 g., 8 atoms), and the mixture refluxed on the water-bath in a stream of dry nitrogen for 4 hours. After this time no apparent change had taken place and ethyl acetate (2.5 c.c.) was added to catalyse the reaction. After a further 4 hours' refluxing, ethyl acetate (2.5 c.c.) was again added and the refluxing continued for 11 hours, by which time the sodium wire had broken up and a heavy white precipitate had collected. The mixture was filtered and the ether removed by distillation in an apparatus similar to that described for 2-phenyl-1:2:3:4-tetrahydroisarsinoline (Holliman and Mann, *loc. cit.*). The residual oil was distilled under reduced pressure: after a preliminary, low-boiling fraction, a small amount of distillate was collected at 150–180°/0.1 mm. The latter possessed a pronounced phosphine-like odour and reacted with methyl iodide to give an oily product. When dissolved in benzene and treated with *p*-chlorophenacyl bromide, no precipitation took place, but evaporation to dryness, dissolution in alcohol, and subsequent addition of ether caused the precipitation of a white solid which was purified by precipitation with ether from an alcoholic solution. The phosphonium bromide then had m. p. 227–230° (Found: C, 60.65; H, 5.1; Cl, 7.7; Br, 17.5. $C_{24}H_{23}OClBrP$ requires C, 60.8; H, 4.8; Cl, 7.5; Br, 16.9%. The Cl and Br were calculated from a total halogen estimation on the assumption that they were present in equi-atomic proportions).

From the low-boiling distillate, unchanged *p*-tolylidichlorophosphine, b. p. 70–80°/0.25 mm., was isolated, together with a fraction at 30°/0.5 mm. The latter boiled at 162° at atmospheric pressure and proved to be *o*-ethyltoluene (Found: C, 89.6; H, 9.6. Calc. for C_9H_{12} : C, 90.0; H, 10.0%).

Reaction of *o*-2-Bromoethylbenzyl Bromide with Magnesium.—Preliminary experiments showed that the dibromide would not react with magnesium under the usual conditions of the Grignard reaction. The dibromide (13.9 g.) and ethyl bromide (5.45 g., 1 mol.) were dissolved in dry ether (60 c.c.), and a portion (5 c.c.) of this solution was added to magnesium turnings (3.6 g., 3 atoms) under ether (20 c.c.). After the addition of a crystal of iodine reaction soon set in and the rest of the bromide solution was added so that the ether was kept gently boiling without external chilling. When the whole of the solution had been added, the mixture was refluxed for 6 hours in an atmosphere of nitrogen, after which time only a small amount of magnesium remained. The cooled mixture was poured, in small portions, on powdered solid carbon dioxide (100 g.) covered with dry ether (100 c.c.). After being set aside overnight the product was hydrolysed with dilute sulphuric acid, the ethereal layer separated, and washed with water. The ethereal solution was shaken with 5% sodium hydroxide solution, and the alkaline extract then boiled to remove ether. Acidification of the cooled solution caused precipitation of an oil which crystallised after 2 hours' keeping at 0°. The solid was collected, washed with water, and dried (5.4 g.). Extraction of this solid with boiling petrol (b. p. 80–100°) gave an insoluble residue (1.4 g.), m. p. 168–185°, which after repeated crystallisation from ethyl acetate gave a white, micro-crystalline solid, m. p. 198–200.5° (Found: C, 72.5; H, 6.8. $C_{20}H_{22}O_4$ requires C, 73.5; H, 6.8%). Evaporation of the petrol filtrate left an oil (3.9 g.) which readily crystallised, and when recrystallised twice from water afforded colourless crystals, m. p. 84–85°, raised by another recrystallisation from petrol (b. p. 60–80°) to 85–86°. This compound was evidently *o*-ethylphenylacetic acid (Found: C, 73.0; H, 6.9. Calc. for $C_{10}H_{12}O_2$: C, 73.1; H, 7.4%). Mayer and English (*Annalen*, 1918, **417**, 72) give m. p. 83.5°.

Reaction of *o*-2-Bromoethylbenzyl Bromide with Diarylalkylphosphines.—Phenyl-*p*-tolylethylphosphine (Wedekind, *Ber.*, 1912, **45**, 2935) in ethereal solution was treated with *o*-2-bromoethylbenzyl bromide (1 mol.) also in ethereal solution. The oily precipitate which gradually formed eventually crystallised and was filtered off and cautiously washed with alcohol. The phosphonium bromide (X; R = Et) melted at 146–148° with softening from 143° (Found: C, 56.3; H, 5.3; Br, 31.4. $C_{24}H_{27}Br_2P$ requires C, 56.9; H, 5.3; Br, 31.6%). The thermal decomposition of this salt gave only non-crystalline products from which no crystalline derivative could be prepared.

By a similar method, the phosphonium salt (X; R = Me) was prepared from phenyl-*p*-tolyl-methylphosphine (Radcliffe and Brindley, *loc. cit.*) and the dibromide. It was recrystallised from alcohol-ether and then melted at 185–186° (Found: C, 55.9; H, 5.2; Br, 31.9. $C_{22}H_{25}Br_2P$ requires C, 56.1; H, 5.1; Br, 32.5%). Again thermal decomposition under different conditions always gave glassy products which could neither be crystallised nor converted into crystalline derivatives.

***o*-Bromobenzyl Methyl Ether** (XII).—*o*-Bromobenzyl bromide (200 g.) was cautiously added to a thoroughly chilled solution of sodium (20 g., 1.08 atoms) in methyl alcohol (600 c.c.). The mixture was refluxed on the water-bath for a short time, and the methyl alcohol then distilled off, a current of air being drawn through the mixture to avoid serious bumping. Sodium bromide was dissolved from the residue by the addition of water (500 c.c.), and the insoluble oil extracted with ether. The aqueous layer was again extracted, the combined extracts washed with water, and dried (CaCl₂). After removal of the solvent the residue was fractionated under reduced pressure: yield 145 g. (90%), b. p. 106–107°/16 mm. (Found: C, 47.9; H, 5.5; Br, 40.5. C_8H_9OBr requires C, 47.75; H, 4.5; Br, 39.8%).

***o*-2-Hydroxyethylbenzyl Methyl Ether** (XIII).—The Grignard reagent from *o*-bromobenzyl methyl ether was prepared by running a solution of the bromo-compound (145 g.) and ethyl bromide (26 g., 0.33 mol.) in dry ether (300 c.c.) on to magnesium (35 g., 2.02 atoms) under ether (100 c.c.), the rate of addition being adjusted so that gentle refluxing was maintained whilst the mixture was vigorously stirred. [The magnesium used in this preparation was activated by heating with iodine as described by Holliman and Mann (*loc. cit.*)] When the addition was complete, the mixture was refluxed on the water-bath for 2 hours, then chilled in an ice-salt freezing mixture, and a solution of ethylene oxide (100 g., 3.15 mols.) in ether (600 c.c.) slowly added during 4 hours. The product was set aside overnight

at room temperature, and then chilled in ice-water and hydrolysed cautiously with dilute sulphuric acid (850 c.c., 1 vol. acid : 9 vols. water). The ethereal layer was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent left an oil which was fractionated under reduced pressure yielding the ether (XIII), b. p. 152–154°/14 mm., as the main fraction: yield 64 g. (53%). The product was refracted several times but even so gave an unsatisfactory analysis (Found: C, 74.9; H, 8.2. $\text{C}_{10}\text{H}_{14}\text{O}_2$ requires C, 72.3; H, 8.4%). For characterisation a sample was therefore warmed with phenyl isocyanate to give 2-*o*-methoxymethylphenylethyl *N*-phenylcarbamate as an oil which crystallised on treatment with petrol (b. p. 60–80°). Two recrystallisations from petrol gave colourless crystals, m. p. 64–65° (Found: 72.4; H, 6.5; N, 4.95. $\text{C}_{17}\text{H}_{19}\text{O}_3\text{N}$ requires C, 71.6; H, 6.7; N, 4.9%). As in the synthesis of the corresponding ethyl ether (Holliman and Mann, *loc. cit.*), a forerun of 2-bromoethyl alcohol was also obtained.

***o*-2-Chloroethylbenzyl Methyl Ether (XIV).**—A solution of *o*-2-hydroxyethylbenzyl methyl ether (182 g.) and dry pyridine (87 g., 1 mol.) in chloroform (220 c.c.) was vigorously stirred and chilled in ice-water whilst thionyl chloride (131 g., 1 mol.) was slowly added during 2 hours. The mixture was then transferred to the water-bath and refluxed with vigorous stirring for 2.5 hours; during the initial stages of this process the mixture became cloudy, an oil separated, and sulphur dioxide was evolved, but after 1.5 hours a clear solution had again been produced. After chilling, the chloroform solution was repeatedly washed with water, then with a 1% solution of sodium hydroxide, and finally with water before drying over calcium chloride. The solvent was removed by distillation at atmospheric pressure, and the residue then fractionated under reduced pressure, the fraction, b. p. 131°/14 mm., being collected (146 g., 72%). Upon refractionation the pure *o*-2-chloroethylbenzyl methyl ether was obtained, b. p. 131°/14 mm. (Found: C, 65.0; H, 7.5. $\text{C}_{10}\text{H}_{13}\text{OCl}$ requires C, 65.05; H, 7.0%).

Reaction of *o*-2-Chloroethylbenzyl Methyl Ether with Magnesium.—*o*-2-Chloroethylbenzyl methyl ether (9.2 g.) and ethyl bromide (2.72 g., 0.5 mol.) in dry ether (40 c.c.) were slowly added to magnesium turnings (1.8 g., 1.5 atoms). The reaction was started by gentle warming and then proceeded vigorously whilst the bromide solution was slowly added. After the addition was complete, the mixture was refluxed during 2 hours. The cooled solution was carefully poured on powdered solid carbon dioxide (80 g.) under ether (40 c.c.). The mixture was allowed to attain room temperature, treated with a further quantity of solid carbon dioxide (40 g.), and then set aside during 24 hours. Hydrolysis was performed at 0° with dilute sulphuric acid (100 c.c., 1 vol. acid : 9 vols. water), the ethereal layer separated, washed with water, and extracted with 5% sodium hydroxide solution (100 c.c.). The alkaline filtrate was evaporated to about half bulk, boiled with charcoal, and filtered. Acidification of the chilled filtrate gave a white precipitate which was collected on the filter, washed with water, and dried: yield 5.6 g. (58%) of the practically pure β -*o*-methoxymethylphenylpropionic acid, m. p. 76–78°. Recrystallisation from petrol gave colourless crystals, m. p. 77–78° (Found: C, 68.35; H, 6.95. $\text{C}_{11}\text{H}_{14}\text{O}_3$ requires C, 68.6; H, 7.2%).

Phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine (as XV).—The Grignard reagent was prepared from *o*-2-chloroethylbenzyl methyl ether (9.2 g.), ethyl bromide (2.72 g., 0.5 mol.) in ether (40 c.c.), and magnesium turnings (1.8 g., 1.5 atoms) as described above. With a stream of dry nitrogen passing through the apparatus, the mixture was refluxed for 2.5 hours and then chilled in ice-water, whilst, with vigorous stirring, a solution of phenyl-*p*-bromophenylchlorophosphine (16.5 g., 1.1 mols.) (Davies and Mann, *J.*, 1944, 279) in dry ether (60 c.c.) was slowly added during 20 minutes. After refluxing for 3 hours the mixture was set aside overnight with a stream of nitrogen passing through the apparatus to minimise atmospheric oxidation. The mixture was chilled and vigorously stirred whilst being hydrolysed by addition of a solution of ammonium chloride (25 g.) in water (100 c.c.). The nitrogen was now replaced by carbon dioxide and, using a suitable apparatus, the contents of the reaction flask were forced over by gas pressure, through a sintered-glass funnel into a separating funnel from which the air had been displaced by the passage of carbon dioxide. The aqueous layer was run off, and the ethereal layer washed with water and then dried (Na_2SO_4) in an inert atmosphere. The solution, filtered from the drying agent in carbon dioxide, was distilled from the water-bath in a stream of nitrogen. When all the ether had been removed, the residue was fractionated under reduced pressure, the fractions, b. p. 130–160°/0.1–0.2 mm. and 200–230°/0.1–0.2 mm., being collected. The former was a colourless oil, presumably phenyl-*p*-bromophenylethylphosphine (3.1 g., representing 42.5% of the theoretical based on the ethyl bromide used). The high-boiling fraction was a viscous, green, highly refractive oil which upon redistillation gave the pure phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine as a viscous, almost colourless oil, b. p. 214–216°/0.1 mm. (Found: C, 63.1; H, 5.5; Br, 18.65. $\text{C}_{22}\text{H}_{22}\text{OBrP}$ requires C, 63.9; H, 5.4; Br, 19.3%; yield, 12 g., 59%).

Methiodide. An ethereal solution of the tertiary phosphine, treated with methyl iodide, rapidly deposited a colourless, sticky semi-solid. The solvent was decanted off, and the gum dissolved in alcohol, ether then being added until a slight cloudiness was produced. On standing for some days, a colourless crystalline precipitate collected; this was filtered off and recrystallised from alcohol, two recrystallisations sufficing to give the pure methiodide as colourless crystals, m. p. 167–168° (Found: C, 49.6; H, 4.8; Br, 14.2; I, 22.5. $\text{C}_{22}\text{H}_{22}\text{OBrIP}$ requires C, 49.7; H, 4.5; Br, 14.4; I, 22.9%). The Br and I were calculated from a total halogen estimation, it being assumed they were present in equi-atomic proportion).

2-Phenyl-2-*p*-bromophenyl-1 : 2 : 3 : 4-tetrahydroisosphospholinium Bromide (as VI).—A stream of anhydrous hydrogen bromide was generated by passing a mixture of bromine vapour with excess of hydrogen through a heated combustion tube and completely freed from free bromine by passage over metallic copper. This gas stream was passed through a solution of phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine (6.7 g.) in glacial acetic acid (275 c.c.) and constant-boiling hydrobromic acid (275 c.c.) maintained at 120° in an oil-bath. After 2 hours the acetic acid and hydrobromic acid were distilled off in a vacuum, leaving a brown viscous mass. The latter was dissolved in alcohol (25 c.c.) and again evaporated to dryness under reduced pressure, finally being dried in a vacuum over concentrated sulphuric acid and sodium hydroxide. The gum failed to crystallise and was therefore dissolved in alcohol (100 c.c.), boiled with charcoal, and filtered. The filtrate was concentrated

(40 c.c.), and chilling in ice-water then gave a crystalline precipitate which was collected, washed with alcohol, and dried: m. p. 125—130°. Recrystallisation from ethyl alcoholic ethyl acetate gave colourless crystals of the pure *bromide*, m. p. 137—149° to a viscous cloudy liquid which resolidified and melted at 218—221°, this behaviour persisting in spite of repeated recrystallisation (Found: C, 54.3; H, 4.3; Br, 35.4. $C_{21}H_{19}Br_2P$ requires C, 54.55; H, 4.1; Br, 34.6%). A sample was heated in an oil-bath to the lower m. p. and the heating continued until solidification set in: analysis then indicated that no significant change had taken place (Found: C, 53.6; H, 4.21; Br, 35.7%).

A hot aqueous solution of the phosphonium bromide, treated with an aqueous solution of sodium picrate, gave an emulsion from which a crystalline precipitate was readily obtained. Recrystallisation from alcohol gave the pure *picrate* as glistening, elongated, yellow plates, m. p. 186—187° (Found: C, 53.3; H, 3.4; N, 6.9. $C_{21}H_{19}O_7N_2BrP$ requires C, 53.1; H, 3.4; N, 6.9%).

Conversion of the phosphonium bromide into the *d*-bromocamphorsulphonate, the *d*-hydrogen tartrate, the *l*-*N*-1-phenylethylphthalamate and the *d*-camphorsulphonate was accomplished by the usual method employing the silver salt of the appropriate acid. Of these phosphonium salts only 2-phenyl-2-*p*-bromophenyl-1:2:3:4-tetrahydroisophospholinium *d*-camphorsulphonate was obtained crystalline, m. p. 206—212° (Found: C, 60.1; H, 5.8. $C_{23}H_{24}O_4BrSP$ requires C, 60.6; H, 5.6%). A 0.326% solution in ethyl alcohol had $\alpha_D^{25} = +0.21^\circ$, $[M]_D^{25} = +98.7^\circ$; the m. p. and rotation underwent no significant change upon recrystallisation of the salt from ethyl-alcoholic ether.

Phenyl-p-anisyl-2-(o-methoxymethylphenyl)ethylphosphine (as XV).—This phosphine was prepared in a precisely similar manner to that described for its *p*-bromophenyl analogue described above, phenyl-*p*-anisylchlorophosphine (13.9 g., 1.1 mols.), prepared according to the method of Davies and Mann (*J.*, 1944, 281), being used in place of the phenyl-*p*-bromophenylchlorophosphine. After the small preliminary fraction of phenyl-*p*-anisylethylphosphine, the required *phosphine* was collected at 215—225°/0.1 mm. Refractionation gave the pure phosphine, b. p. 208°/0.05 mm. (Found: C, 76.1; H, 7.2. $C_{22}H_{22}O_2P$ requires C, 75.75; H, 6.9%). yield, 11.8 g., 65%.

In ethereal solution, the phosphine rapidly combined with methyl iodide at room temperature, the *methiodide* being precipitated as a gummy mass. The supernatant ethereal solution was decanted off, and the residue recrystallised from alcohol to give the pure salt as colourless crystals, m. p. 120°—121° (Found: C, 57.1; H, 5.4; I, 25.9. $C_{22}H_{22}O_2IP$ requires C, 56.9; H, 5.6; I, 25.1%).

2-Phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium *Bromide* (as VI).—Demethylation, bromination, and ring closure of phenyl-*p*-anisyl-2-(o-methoxymethylphenyl)ethylphosphine was carried out in glacial acetic acid-hydrobromic acid mixture as described in the preparation of the 2-phenyl-2-*p*-bromophenyl analogue; in this case, however, the heating at 120° was for 5 hours. Removal of the glacial acetic and hydrobromic acids under reduced pressure left a crystalline solid which was treated with a small amount of alcohol, filtered off, and washed with ether: m. p. 285—286°. Recrystallisation from methyl alcohol gave colourless crystals, m. p. 287—287.5°, of the pure 2-phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium *bromide*, demethylation of the *p*-anisyl group also having taken place (Found: C, 63.4; H, 5.2; Br, 21.0. $C_{21}H_{20}OBrP$ requires C, 63.15; H, 5.1; Br, 20.0%). yield 75%.

A solution of the phosphonium bromide (0.5 g.) in pyridine (8 c.c.) was treated with acetic anhydride (2 c.c.) and the mixture refluxed for 1 hour. The hot solution was filtered from the slight amount of solid which had separated, and the filtrate on cooling gave a crystalline precipitate, which was collected and washed with pyridine followed by ether. The acetyl derivative was much more soluble in alcohol than the original phosphonium bromide, and recrystallisation was accomplished from alcoholic ethyl acetate; the colourless crystals obtained, m. p. 100—103°, were deliquescent when exposed to the air, after 48 hours the m. p. having fallen to ca. 50°. The twice recrystallised 2-phenyl-2-*p*-acetoxyphenyl-1:2:3:4-tetrahydroisophospholinium *bromide* was dried by heating at 80°/1 mm. for 3 hours before analysis (Found: C, 62.2; H, 5.6; Br, 17.2. $C_{23}H_{22}O_4BrP$ requires C, 62.6; H, 5.0; Br, 18.1%).

dl-2-Phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium *d*-Bromocamphorsulphonate.—A methyl-alcoholic solution of the bromide was mixed with a similar solution of silver *d*-bromocamphorsulphonate (1 mol.). After boiling for a few minutes, the solution was filtered from the precipitated silver bromide and evaporated to dryness in a vacuum at room temperature. The residual oil was gently warmed with benzene, scratching then readily inducing crystallisation: the m. p. of the unrecrystallised material was 137—147° with softening from 130°, and a 1.015% ethyl-alcoholic solution had $\alpha_D^{17} + 1.94^\circ$, $[M]_D^{17} + 300^\circ$. Two recrystallisations from ethyl alcohol-ethyl acetate raised the m. p. to 145—152° but no change in rotatory power was observed: for a 1.008% ethyl-alcoholic solution, $\alpha_D^{18} + 1.92^\circ$, $[M]_D^{18} + 300^\circ$ (Found: C, 58.7; H, 6.0; Br, 13.6. $C_{21}H_{20}O_4SBP$ requires C, 59.1; H, 5.5; Br, 12.7%).

The salt was next recrystallised repeatedly from isopropyl alcohol. After five such recrystallisations the m. p. was 116—125° in spite of intensive drying at 80°/0.1 mm. Since a 1.030% ethyl-alcoholic solution had $\alpha_D^{19} + 2.00^\circ$, $[M]_D^{19} + 305^\circ$, it was considered that resolution was not proceeding.

Repeated recrystallisation from acetone gave a sample which consistently melted at 135—140° with previous softening. After four recrystallisations the salt in 1.080% ethyl-alcoholic solution had $\alpha_D^{19} + 2.005^\circ$, $[M]_D^{19} + 313^\circ$. The phosphonium bromide was precipitated from an ethyl-alcoholic solution of this sample of the *d*-bromocamphorsulphonate by treatment with an alcoholic solution of sodium bromide at 0°. A methyl-alcoholic solution (0.362%), however, showed no optical activity.

The *d*-camphorsulphonate was prepared by a similar method from silver *d*-camphorsulphonate. The gum remaining after the removal of the solvents was thoroughly freed from methyl alcohol by evacuation at 0.1 mm. for a prolonged period and then dissolved in acetone. After boiling with charcoal the filtered solution was set aside at 0°. After several days practically the whole of the solute had separated as a microcrystalline powder insoluble in hot acetone. This salt was apparently the dl-phosphonium *d*-camphorsulphonate, m. p. 153—158° (Found: C, 67.0; H, 6.3; S, 5.8. $C_{21}H_{20}O_4SP$ requires C, 67.6; H, 6.4; S, 5.8%). 26 G. of the phosphonium bromide gave 27 g. (representing 75% of the theoretical) of this salt after the above process of isolation, and a 0.991% ethyl-alcoholic solution had $\alpha_D^{19} + 0.74^\circ$, $[M]_D^{19} + 102^\circ$. It was far too soluble in methyl, ethyl, or *n*-propyl alcohol for

recrystallisation, and the use of *sec.*-butyl alcohol failed to change either the m. p. or the rotatory power. The salt (25 g.) was boiled with ethyl acetate (150 c.c.), in which it was insoluble, and alcohol carefully added until complete solution was obtained (41.5 c.c. required): after boiling with charcoal and filtering, the solution was set aside for a few days, whereupon clusters of needles began to separate. Crystallisation was allowed to proceed at 2° for three days, and the salt was then collected and washed, first with ethyl acetate-ethyl alcohol (4:1) and then with ethyl acetate: 6.4 g. of colourless needles, m. p. 171–172.5°, were obtained, and a 0.985% solution in alcohol had $\alpha_D^{25} + 0.79^\circ$, $[M]_D^{25} + 110^\circ$. The mother-liquor upon dilution with ethyl acetate (50 c.c.) gave a second crop (5.3 g.), m. p. 153–157°, a 0.990% alcoholic solution having $\alpha_D^{25} + 0.75$, $[M]_D^{25} + 104^\circ$. Evaporation to dryness under reduced pressure gave a third fraction (12 g.), m. p. 142–151°, $\alpha_D^{25} + 0.71^\circ$, $[M]_D^{25} + 98.4^\circ$ for a 0.993% alcoholic solution.

Three more recrystallisations of the first crop from ethyl acetate-ethyl alcohol raised the m. p. of the salt to 174–175°, the optical constants then being $\alpha_D^{25} + 0.81^\circ$, $[M]_D^{25} + 113.5^\circ$ for a 0.983% alcoholic solution. Further treatment failed to alter these values and the salt was evidently the optically pure *d*-phosphonium *d*-camphorsulphonate (Found: C, 68.0; H, 6.46%).

d-2-Phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisosphosphinolinium Bromide.—The *d*-phosphonium *d*-camphorsulphonate (2.2 g.) was dissolved in alcohol (20 c.c.), and the solution cooled to 0° whilst a similarly chilled solution of calcium bromide (5 g.) in alcohol (10 c.c.) was rapidly added. Stirring and scratching caused precipitation of the crystalline bromide, which was collected, and washed with two portions of 5 c.c. and three of 2.5 c.c. of alcohol. 1.5 G. (94%) of the pure bromide were obtained, m. p. 268–270° with softening from 263° (Found: C, 62.6; H, 5.0; Br, 20.7. $C_{21}H_{20}OBrP$ requires C, 63.15; H, 5.1; Br, 20.0%). A 1.029% solution in aqueous alcohol (2 vols. alcohol: 1 vol. water) had $\alpha_D^{25} + 0.34^\circ$, $[M]_D^{25} + 32.9^\circ$.

Recrystallisation from alcohol failed to affect the m. p. or to cause any significant change in the rotatory power: for a 1.010% solution in aqueous alcohol, $\alpha_D^{25} + 0.34^\circ$, $[M]_D^{25} + 33.7^\circ$ (values for other wave-lengths for a 1.029% solution of this recrystallised material are given in the table on p. 1638) (Found: C, 62.7; H, 4.9; Br, 20.15%).

With methyl alcohol as solvent a marked decrease in rotatory power was observed: a 1.032% solution had $\alpha_D^{25} + 0.05^\circ$, $[M]_D^{25} + 4.8^\circ$. The bromide was recovered from the solution by evaporation in a vacuum and a 0.941% solution of this material in aqueous alcohol had $\alpha_D^{25} + 0.31^\circ$, $[M]_D^{25} + 32.9^\circ$.

The Phosphonium l-Camphorsulphonate.—The phosphonium bromide was recovered from the second and the third fraction of the *d*-camphorsulphonate by precipitation with calcium bromide as described above, and was then converted into the *l*-camphorsulphonate by the usual method. The glass obtained by evaporation of the methyl-alcoholic solution was crystallised from acetone and then had m. p. 152–157°. When recrystallisation was attempted from ethyl acetate-ethyl alcohol, in the proportions used for the *d*-camphorsulphonate, the hot solution initially obtained began to deposit a crystalline precipitate and considerably more alcohol was required before solution could be re-obtained [14 g. of the salt in ethyl acetate (90 c.c.) required 47 c.c. of alcohol]. On cooling, a crystalline precipitate of *l*-camphorsulphonate rapidly separated: 11.8 g., m. p. 170–172°. This had $\alpha_D^{25} - 0.73^\circ$, $[M]_D^{25} - 102^\circ$ for a 0.950% solution in alcohol (Found: C, 68.1; H, 6.3. $C_{21}H_{20}O_2SP$ requires C, 67.6; H, 6.4%). Evaporation of the mother-liquors left a solid residue, m. p. 165–168°, $\alpha_D^{25} - 0.72^\circ$, $[M]_D^{25} - 101^\circ$ for a 0.945% alcoholic solution.

The phosphonium bromide was regenerated from a sample of the first crop; this had m. p. 286–288° and proved to be optically inactive in aqueous-alcoholic solution, in which solvent it was considerably less soluble than the *d*-phosphonium bromide described above.

Repeated attempts to recrystallise the *l*-camphorsulphonate from ethyl acetate-ethyl alcohol showed that it was much less soluble than the *d*-phosphonium *d*-camphorsulphonate, and a product, m. p. 170–172°, was always obtained. It was redissolved in methyl alcohol, the solution taken to dryness, and the glass crystallised from acetone in the hope that the low-melting form could be again obtained, but such methods led invariably to a product, m. p. 170–172°, evidently a partial racemate of the *dl*-phosphonium *l*-camphorsulphonate. In a similar way, further preparations of the *d*-camphorsulphonate led to a high-melting product from which the inactive bromide, m. p. 286–288°, was regenerated.

We are indebted to Mr. F. C. Baker for a considerable amount of assistance in the preparation of chlorophosphines.

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[Received, February 10th, 1947.]

327. Reduction by Dissolving Metals. Part V.

By ARTHUR J. BIRCH.

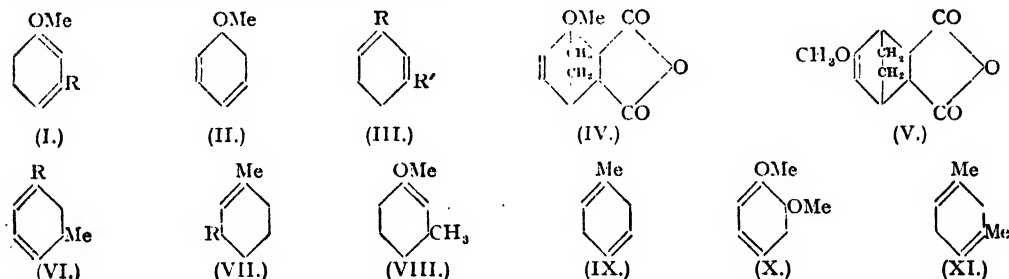
Potassium amide in liquid ammonia conjugates the double bonds of 2:5-dihydroanisoles with formation of 2:3-dihydroanisoles, which give adducts with maleic anhydride and are reduced by sodium in ammonia chiefly to alkylcyclohexenes, but by sodium and alcohol in ammonia chiefly to alkyltetrahydroanisoles. With alkyl-2:5-dihydrobenzenes, instead of the conjugated dienes, the products are chiefly the alkylbenzenes, and the conjugated compound 4:5-dihydro-*m*-xylene gives *m*-xylene under the same conditions. Also observed are the transformations: 2:4-dimethylhexa-1:5-diene \rightarrow 2:4-dimethylhexa-2:4-diene; oct-1-ene \rightarrow oct-2-ene; 4-phenylbut-1-ene \rightarrow 4-phenylbut-2-ene; 3-butoxy-2-methylpropene \rightarrow 1-butoxy-2-methylpropene; 3-methoxycyclohexene \rightarrow a mixture of cyclohexene and benzene; a number of hydrocarbons are unchanged.

The bond migrations are postulated as taking place through anions formed by loss of a proton from an allyl position. The theory is related to the effects of alkyl substitution on the ease of

the process, and applied to a consideration of some reduction phenomena with sodium in ammonia and with calcium hexammine.

IN Part III (*J.*, 1946, 593) it was found that the $\alpha\delta$ -dihydro-derivatives obtained by the reduction with sodium and alcohol in liquid ammonia of methoxyalkyl-, dimethylaminoalkyl-, and alkyl-benzenes were further reduced by sodium and ammonia or by calcium hexammine. Intermediate conjugation of the double bonds was postulated as taking place through a mesomeric anion formed by loss of a proton to the anionoid reagent (either sodium, or calcium hexammine, or the sodium or calcium amide formed in increasing amount as the reaction proceeds). Farmer, Koch, and Sutton (*J.*, 1943, 545) have postulated a similar intervention of mesomeric allylic radicals to explain the formation of conjugated peroxides from non-conjugated dienes in oxidation reactions.

Conjugated compounds have now been produced from the methoxyalkyl- $\alpha\delta$ -dihydrobenzenes by the action of the amides of sodium or potassium in liquid ammonia (the latter preferred because of its solubility); the deep red-brown colour of the solution confirms the formation of a mesomeric carbanion in the process. The products (*e.g.*, I) were identified as conjugated by the formation of crystalline maleic anhydride adducts, by their light absorption at λ_{\max} , *ca.* 2700 Å., and by their ready reduction with sodium and alcohol in ammonia. They must have a disposition of double bonds relative to the methoxyl group of type (I) rather than (II) or (III, R = OMe). Acid hydrolysis produced unsaturated ketones, rather than hydrocarbons, thus eliminating (II), and the maleic anhydride adducts did not behave as the enol ethers of ketones, and were therefore of type (IV) corresponding to (I) rather than of type (V) corresponding to (III, R = OMe). Also, the product from 2:5-dihydro-*p*-tolyl methyl ether must be 2:3-dihydro-*p*-tolyl methyl ether since it gave rise to the 2:4-dinitrophenylhydrazones of 4-methylcyclohex-3- rather than -2-enone.



The conjugated compound from 2:5-dihydro-*m*-tolyl methyl ether is formulated as (I, R = Me) since acid hydrolysis gave 3-methylcyclohex-2-enone, not the alternative 5-methylcyclohex-2-enone to be expected from (VI, R = OMe). Further confirmation came from its reduction products. Sodium and alcohol in ammonia gave a little 1-methylcyclohexene (VII, R = H) and preponderantly 1-methoxy-3-methylcyclohexene (VIII), acid hydrolysis of which produced 3-methylcyclohexanone, and permanganate oxidation α -methyladipic acid. Sodium in ammonia gave mainly (VII, R = H) and a little (VIII). The hydrocarbons similarly obtained from the dihydro-*o*- and -*p*-tolyl methyl ethers were identified by their infra-red absorption spectra as mixtures of methylcyclohexenes: *ortho*-, the 4-methyl- two parts, and the 1- and 3-methyl one part each; *para*-, one part each of the 1-, 3-, and 4-methyl. The 2:5-dihydro-derivatives from 3:5-dimethyl- and 2:6-dimethyl-anisole gave by the prolonged action of sodium in ammonia (doubtless with intermediate conjugation) small amounts of 1-methoxy-3:5- and -2:6-dimethylcyclohexene (hydrolysed by acid to 3:5-dimethyl- and 2:6-dimethyl-cyclohexanone) together with the same hydrocarbon, identified as 2:4-dimethylcyclohexene by comparison of its derivatives with those obtained from an authentic specimen. 1:2-Dimethoxy-3:6-dihydrobenzene gave anisole by the action of potassium amide in ammonia, probably by way of the intermediate (X).

The formation of conjugated derivatives of type (I) can be explained by assuming that a proton is removed from the CH₂ adjacent to the methoxyl group, and that the anion then adds a proton with the final result of pivoting the enol double bond about this group. This is particularly clearly shown by the formation of (I, R = Me) rather than (VI, R = OMe) from dihydro-*m*-tolyl methyl ether. Some dehydrogenation which accompanies the isomerisation may be explained by loss of a hydrogen anion from the intermediate salt (compare the hydrocarbons on p. 1644).

Addition of the alkyl dihydrobenzenes such as 2 : 5-dihydrotoluene (IX) or 2 : 5-dihydro-*m*-xylene (XI) to potassium or sodium amide in liquid ammonia gave a red colour, but the recovered product contained little, if any, of the conjugated diene, the chief constituent being the aromatic hydrocarbon together with a little of the alkyl tetrahydrobenzene and polymeric material. The product obtained by acting on 2 : 5-dihydrotoluene with sodium amide for a short time gave rise to a trace of a maleic anhydride adduct, probably derived from 1-methylcyclohexa-1 : 3-diene, since it was not identical with that obtained from 1-methylcyclohexa-1 : 5-diene. That cyclohexa-1 : 3-dienes themselves can be dehydrogenated by the reagent was shown by the production of *m*-xylene from 4 : 5-dihydro-*m*-xylene, the red colour of the intermediate ion being visible in this case also. These ions must be similar in type to those from the unconjugated dienes, and both can assume the stable aromatic configuration by the expulsion of a hydrogen anion. The dehydrogenation may be compared with the formation of naphthalene and lithium hydride by the action of phenyl lithium on 1 : 4-dihydronaphthalene (Gilman and Bradley, *J. Amer. Chem. Soc.*, 1938, 60, 2333). The source of the small amount of tetrahydrobenzene derivative in the aromatic product is not certain, but in view of the small reducing power of sodium hydride (Swamer and Hauser, *J. Amer. Chem. Soc.*, 1946, 68, 2647) it may have been present in the starting material.

The formation of a considerable proportion of tetrahydrobenzene derivative by the action of sodium in ammonia or of calcium hexamine on the unconjugated compound must have been due to reduction of the conjugated compound as it was produced; this also agrees with the fact that less polymeric material was formed. Even here, however, some aromatic material appeared (see 2 : 5-dihydrotoluene). It is noteworthy that the same ratio of 1- to 3-methylcyclohexene was obtained from toluene or 2 : 5-dihydrotoluene, irrespective of which reduction process was employed, and that reduction of 4 : 5-dihydro-*m*-xylene (III; R, R' = Me) gave 1 : 3-dimethylcyclohexene (VII, R = Me) already obtained from *m*-xylene and 2 : 5-dihydro-*m*-xylene (Part III, *loc. cit.*). The fact that alkylcyclohexenes are unaltered by the reagents makes it possible to draw conclusions about the reduction intermediates from the position of the double bond in these products.

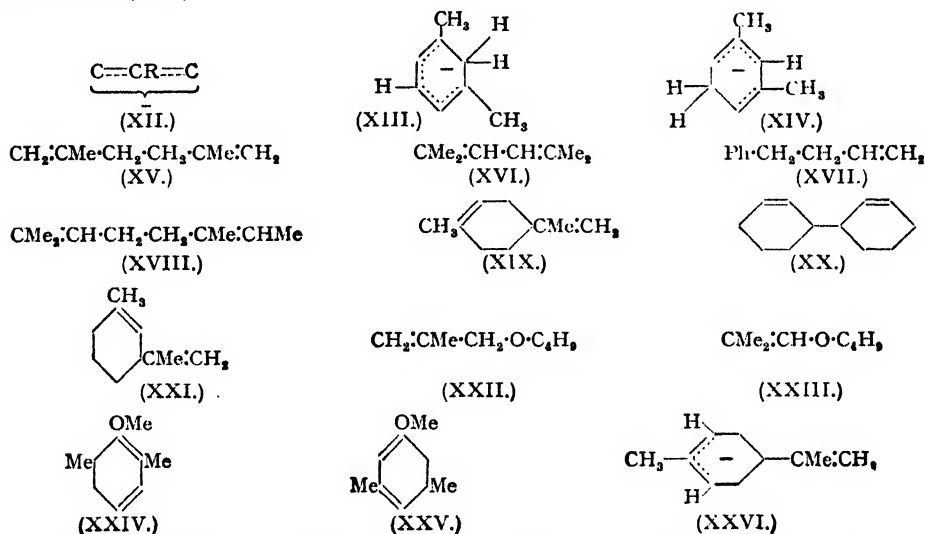
The reason for the observed difference in the rate of dehydrogenation of the dihydroanisole and dihydrobenzene derivatives may be due to the higher energy of the anions with the latter due to the inductive effect of the alkyl groups; this may be correlated with the fact that, although some conjugated material was detected in the case of dihydrotoluene, none was observed with the more highly alkylated dihydro-*m*-xylene. That methoxyl groups have a stabilising effect on anions except when the charge is forced to reside on the occupied or para-carbon atoms is clear from a number of results obtained in Part IV (this vol., p. 102) and from the fact that 2-methoxynaphthalene is reduced mainly in the occupied ring.

Hydrocarbon.	Reagent.	Product.
2 : 5-Dihydrotoluene	KNH ₂ , NH ₃	Toluene; methylcyclohexene (tr.)
2 : 5-Dihydro- <i>m</i> -xylene	KNH ₂ , NH ₃	<i>m</i> -Xylene
4 : 5-Dihydro- <i>m</i> -xylene	KNH ₂ , NH ₃	<i>m</i> -Xylene
Oct-1-ene	KNH ₂ , NH ₃	Oct-1-ene, 80%; oct-2-ene, 20%
2 : 5-Dimethylhexa-1 : 5-diene ...	KNH ₂ , NH ₃	2 : 5-Dimethylhexa-2 : 4-diene
4-Phenylbut-1-ene	KNH ₂ , NH ₃	4-Phenylbut-2-ene(?); polymer
3-Methyl-, 1 : 3-dimethyl-, 2 : 4-dimethyl-cyclohexene; <i>d</i> -limonene, <i>d</i> -sylvestrene, methylgeraniolene, 1 : 2 : 3 : 4 : 1' : 2' : 3' : 4'-octahydrodiphenyl	KNH ₂ , NH ₃ or Ca(NH ₂) ₂	Unchanged
2 : 5-Dihydrotoluene	Na, NH ₃	1-Methylcyclohexene, 50%; toluene, 40%; 3-methylcyclohexene, 10%
2 : 5-Dihydrotoluene	Ca(NH ₂) ₂	1-Methylcyclohexene, 80%; 3-methylcyclohexene, 10%
2 : 5-Dihydro- <i>m</i> -xylene	Na, NH ₃ ; Ca(NH ₂) ₂	1 : 3-Dimethylcyclohexene *
4 : 5-Dihydro- <i>m</i> -xylene	Na, EtOH, NH ₃	1 : 3-Dimethylcyclohexene
Toluene	Ca(NH ₂) ₂	1-Methylcyclohexene, 80%; 3-methylcyclohexene, 20%
4-Phenylbut-1-ene	Na, NH ₃	Phenylbutane

* Part III, *loc. cit.*; the constitution of the product is proved in the present paper.

The ability to conjugate depends on the ability to form the alkali-metal salts and therefore on the presence of a relatively acidic hydrogen atom, which, with the cyclohexadienes, is due to stabilisation of the anion resulting from proton removal by resonance of the charge with the ends of the two double bonds. The production of the conjugated compound on addition of a proton to this ion is, of course, due to the lower energy of the double bonds in conjugation. It has

already been pointed out (Part II, *J.*, 1945, 809) that the lower the degree of alkylation of the end carbon atoms of a mesomeric anion of type (XII) the more readily it is formed, *i.e.*, the more acidic the proton whose removal produces it. This is further confirmed by the work of Morton, Brown, Holden, Letsinger, and Margat (*J. Amer. Chem. Soc.*, 1945, **67**, 2224) on the direct metallation of alkylethylenes. These ideas may be applied to predict that the conjugation of 1:3-dimethyl-2:5-dihydrobenzene (XI), which might proceed through (XIII) or (XIV), should take place through the latter, since the negative charges would reside on less alkylated carbon atoms at the ends of the mesomeric system. This is confirmed by the production of 1:3-dimethylcyclohexene (VII, *R* = Me) by sodium in ammonia reduction, since this could hardly be derived from (XIII) through (VI, *R* = Me), and is given by (III; *R* = *R'* = Me) derivable from (XIV).



With compounds having double bonds insulated from one another by two saturated carbon atoms the conditions for migration are less favourable, since removal of a proton in the allyl position gives an anion in which the charge can resonate with only one double bond. The double bond in oct-1-ene was moved in part to the 2-position, and in this case the mesomeric anion has a low degree of alkylation, having at its ends CH_2 and CHR . This is also true of the initial stage of isomerisation of 2:5-dimethylhexa-1:5-diene (XV) to 2:5-dimethylhexa-2:4-diene (XVI) (the compound has also been reduced by means of calcium hexamine; Kazanskii and Glushnev, *Bull. Acad. Sci. U.R.S.S.*, 1938, 1065) and of the isomerisation of 4-phenylbut-1-ene (XVII) to 1-phenylbut-2-ene and a polymer, probably derived from 1-phenylbut-1-ene; (XVII) was also reduced to phenylbutane by the prolonged action of sodium in ammonia. The second unsaturated centre must have some influence, however, since isomerisation in these cases is much readier than with oct-1-ene. Substitution of the hexa-1:5-diene with saturated carbon atoms at the ends of the potential resonating ion, *e.g.*, in methylgeraniolene (XVIII), *d*-limonene (XIX), and 1:2:3:4:1':2':3':4'-octahydrodiphenyl (XX), prevented isomerisation with potassium amide in ammonia or reduction by calcium hexamine; more surprisingly, sylvestrene (XXI) was also unaffected. Several of these compounds should have relatively acidic hydrogen atoms present in methyl groups, but the anion formed by loss of a proton should merely regenerate the starting material. Production of the anion (XXVI) from *d*-limonene would result in re-formation of the starting material in the racemic form; in fact, the rotation was unaltered. This agrees with the observation that the double bond in alkylcyclohexenes was not moved.

3-Butoxy-2-methylpropene (XXII), the resonating anion from which would contain CH_2 and CHR , was isomerised to 1-butoxy-2-methylpropene (XXIII), but no 1-methoxycyclohexene was obtained from 3-methoxycyclohexene, loss of methyl alcohol producing a hydrocarbon analysing for cyclohexadiene. It gave no reaction with maleic anhydride, and its physical properties indicated a mixture of benzene and cyclohexene.*

* *Added in Proof.*—For a further discussion of the relationship between structure and acidity see Birch, Faraday Society Discussion, 1947, "Labile Molecules" (in the press).

Reduction of the conjugated *cyclohexadienes* can be explained by the initial addition of two electrons to the system. With the hydrocarbons the bivalent anions so formed then abstract two protons from the alcohol or ammonia; in the case of the methoxy-compounds this may occur, and is naturally favoured by the presence of more readily available protons from alcohol, or a methoxyl anion may be expelled with addition of another electron and finally two protons to give an alkylcyclohexene. This seems to be confirmed by the fact that 2-ethoxy-3:4-dihydronaphthalene gave with sodium in ammonia, with or without alcohol, tetrahydronaphthalene as the first recognisable product. It also explains the formation of the same dimethylcyclohexene from the dihydro-derivatives of 2:6- and 3:5-dimethylanisole by way of the conjugated (XXIV) and (XXV), which would give the same anion after expulsion of the methoxyl. It is noteworthy that dimethyl-2:5-dihydro-*m*-toluidine did not give rise to any hydrocarbon, the product containing the tetrahydroamine, and this may be correlated with the greater energy of formation of the dimethylamino- than of the methoxy-anion.

It is necessary to determine the positions of addition of nascent hydrogen to asymmetrical alkylcyclohexadienes before further conclusions can be drawn; evidence is already available that it may occur in both the $\alpha\beta$ - and the $\alpha\delta$ -positions.

EXPERIMENTAL.

Alkyl-2:3-dihydroanisoles.—The alkyl-2:5-dihydroanisoles were prepared from the alkylanisoles by reduction with sodium and alcohol in liquid ammonia as described in Part III (*loc. cit.*) under the preparation of the derived ketones. The compounds (10 g.) were conjugated by dissolving them in a solution of potassium amide (from the metal, 2 g.) in ammonia (100 c.c.) and stirring for 1½ hours. Water was then added very cautiously to the dark red solution, the oil taken up in ether, dried (K_2CO_3), and distilled. It is unlikely that conjugation is brought about by the caustic alkali formed during working up, since it could not be accomplished with boiling 15% alcoholic potassium ethoxide. The maleic anhydride adducts were prepared by addition to excess of the anhydride in benzene and 6 hours' standing. Material boiling up to 120°/10 mm. was then removed, the product extracted from polymeric material in the residue with ether and crystallised from benzene-light petroleum with the aid of a little fuller's earth.

The reduction of the conjugated compounds was carried by two methods. (A) A solution of the substance (5 g.) and sodium (4 g.) in ammonia (70 c.c.) was left for 30 minutes, excess of ammonium chloride added, then water (70 c.c.), and the oil separated with the aid of a centrifuge if necessary; owing to the volatility of the methylcyclohexenes in boiling ammonia only 2–2.5 g. of product were obtained. (B) The substance (10 g.) in ammonia (100 c.c.) and alcohol (10 g.) was gradually reduced by the addition of sodium (6 g.) over 3 hours with stirring, and the product worked up as above.

2:5-Dihydroanisole (b. p. 148–150°) gave 2:3-dihydroanisole (6.2 g.), b. p. 145°, n_D^{18} 1.4902, λ_{max} 2690 Å., ϵ_{max} 4560 (Found: C, 76.1; H, 9.2. $C_7H_{10}O$ requires C, 76.4; H, 9.1%). Cold 2:4-dinitrophenylhydrazine sulphate in alcohol indicated a 91% content of dihydro-compound, and the derivative formed, m. p. 140–146°, appeared to be a mixture of the cyclohex-3-enone derivative, m. p. 134°, and the Δ^2 -derivative, m. p. 167°. Brief refluxing with alcoholic sulphuric acid gave the latter. The maleic anhydride adduct had m. p. 91° (Found: C, 63.3; H, 5.8. $C_{11}H_{12}O_4$ requires C, 63.4; H, 5.8%). This was unaffected by Brady's reagent.

Reduced by method (B), 2:3-dihydroanisole gave 1-methoxycyclohexene, b. p. 140–145°, which readily gave rise to cyclohexanone 2:4-dinitrophenylhydrazone, m. p. 156–157°.

The mixture of 3:6- and 2:5-dihydro-*o*-tolyl methyl ether obtained by reduction of *o*-tolyl methyl ether (Parts I and III, *loc. cit.*) gave a compound (chiefly 2:3-dihydro-*o*-tolyl methyl ether?), b. p. 155–160° (Found: C, 77.3; H, 9.3. $C_9H_{12}O$ requires C, 77.4; H, 9.7%). Continuation of the reaction for 5½ hours gave a product, b. p. 165–167°, which appeared to be mainly *o*-tolyl methyl ether (Found: C, 79.1; H, 8.3. Calc. for $C_9H_{10}O$: C, 78.7; H, 8.2%). Reduction of the conjugated diene mixture by method (A) gave a fraction, b. p. 100–104°, shown by its infra-red absorption to contain a mixture of methylcyclohexenes: Δ^2 -two parts, Δ^1 - and Δ^2 -one part each.

2:5-Dihydro-*m*-tolyl methyl ether gave 5:6-dihydro-*m*-tolyl methyl ether, b. p. 165–167° (Found: C, 77.6; H, 9.7. $C_9H_{12}O$ requires C, 77.4; H, 9.7%). The maleic anhydride adduct crystallised from benzene-light petroleum in prisms, m. p. 77° (Found: C, 65.2; H, 6.3. $C_{13}H_{14}O_4$ requires C, 64.9; H, 6.3%). Treatment with 2:4-dinitrophenylhydrazine sulphate in hot alcohol gave the derivative of 3-methylcyclohex-2-enone, m. p. 174–175°. Reduction by method (A) gave chiefly a fraction, b. p. 106–110°, n_D^{18} 1.4500 (Found: C, 87.4; H, 12.5. Calc. for C_9H_{12} : C, 87.5; H, 12.5%). The nitropiperidine, m. p. 146–147°, and its infra-red absorption spectrum showed this hydrocarbon to be 1-methylcyclohexene. A small fraction, b. p. 155–162°, gave rise to the 2:4-dinitrophenylhydrazone of 3-methylcyclohexanone, m. p. 154°, and a few drops of material, b. p. 162–172°, appeared to contain *m*-tolyl methyl ether. Reduction by method (B) gave a trace of a fraction (i) b. p. 110–115°, and mainly 1-methoxy-3-methylcyclohexene (ii), b. p. 156–160°, n_D^{18} 1.4660. Hydrolysis of this by boiling with 10% sulphuric acid for an hour, conversion of the oil into a solid bisulphite compound, and regeneration gave 3-methylcyclohexanone, b. p. 165°; 2:4-dinitrophenylhydrazone m. p. 155°, semicarbazone m. p. 180°. Oxidation of (ii) with potassium permanganate in acetone gave an acid which did not crystallise, but readily formed the dianilide of α -methyladipic acid, m. p. 173° (Found: C, 73.7; H, 7.4. Calc. for $C_{13}H_{22}O_2N_2$: C, 73.5; H, 7.1%). Bouveault and Locquin (*Bull. Soc. chim.*, 1908, 3, 451) give m. p. 174–175°.

2:5-Dihydro-*p*-tolyl methyl ether (b. p. 168–170°) gave 2:3-dihydro-*p*-tolyl methyl ether, b. p. 165–167°, λ_{max} 2720, ϵ_{max} 4060 (Found: C, 77.6; H, 9.7. $C_9H_{12}O$ requires C, 77.4; H, 9.7%), giving

with cold Brady's reagent the 2:4-dinitrophenylhydrazone of 4-methylcyclohex-3-enone, m. p. 122°, converted by hot dilute alcoholic sulphuric acid into the derivative of 4-methylcyclohex-2-enone, m. p. 174°. The maleic anhydride adduct had m. p. 85–86° (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%). Reduction by method (A) gave a hydrocarbon fraction, b. p. 103–105° (Found: C, 87.3; H, 12.7. Calc. for C_8H_{14} : C, 87.5; H, 12.5%). This was shown by its infra-red absorption to contain about one part each of 1-, 3-, and 4-methylcyclohexene. Reduction by method (B) gave chiefly a fraction (1-methoxy-4-methylcyclohexene), b. p. 157–162° (Found: C, 76.0; H, 10.6. $C_8H_{14}O$ requires C, 76.2; H, 11.1%), which on acid hydrolysis and bisulphite purification gave 4-methylcyclohexanone, b. p. 165–167°, semicarbazone m. p. 196°.

In order to investigate the ease of dehydrogenation in this case the conjugation reaction was continued for (i) 2½ hours and (ii) 5½ hours, giving as the products: (i), b. p. 165–167° (Found: C, 77.4; H, 9.8. Calc. for $C_8H_{14}O$: C, 77.4; H, 9.7%), λ_{max} 2720, ϵ_{max} 3640; and (ii), b. p. 165–170° (Found: C, 77.9; H, 9.3. Calc. for $C_8H_{14}O$: C, 77.4; H, 9.7%). The latter by estimation with Brady's reagent showed only about a 50% content of methylidihydroanisole. Dehydrogenation had thus taken place, although to a smaller extent than with the dihydro-*o*-tolyl methyl ether.

2:6-Dihydroveratrole (Part IV, *loc. cit.*) gave rise to anisole, b. p. 145–150°, unaffected by Brady's reagent and demethylated to phenol.

Reduction of 3:5- and 2:6-Dimethylanisole.—These compounds (10 g.) were reduced in ammonia (100 c.c.) with sodium (5 g.) and alcohol (5 g.), a further amount of sodium (5 g.) added, and the mixture left for 10 hours and worked up as usual.

3:5-Dimethylanisole gave (i), b. p. 125–130° (2.4 g.), and (ii), b. p. 185–195°. Fraction (i) gave a good yield of a nitropiperidine as colourless prisms from methyl alcohol, m. p. 146–147° (Found: C, 69.4; H, 10.6. $C_{13}H_{24}ON_2$ requires C, 69.6; H, 10.7%), undepressed by the derivative of 2:4-dimethylcyclohexene. Fraction (ii) seemed to be largely starting material, but reacted with Brady's reagent to give the 2:4-dinitrophenylhydrazone of 3:5-dimethylcyclohexanone, m. p. 155–157° (Found: C, 54.2; H, 6.0. $C_{14}H_{24}O_4N_4$ requires C, 54.7; H, 6.1%). Two stereoisomers are possible, and there is no evidence as to whether one or a mixture was present.

2:6-Dimethylanisole gave (i), b. p. 125–130° (1.1 g.), and (ii), b. p. 160–170° (0.5 g.), together with a higher fraction of starting material. Fraction (i) gave the nitropiperidine, m. p. 146–147°, of 2:4-dimethylcyclohexene. Fraction (ii) gave the 2:4-dinitrophenylhydrazone of 2:6-dimethylcyclohexanone, m. p. 149–150°, also possibly a mixture of stereoisomers (Found: C, 55.0; H, 5.9. $C_{14}H_{24}O_4N_4$ requires C, 54.7; H, 6.1%).

The 2:4-dimethylcyclohexene required for comparison was synthesised by reducing *m*-4-xyleneol with Raney nickel and hydrogen at 150°/100 atm., esterifying the resulting 2:4-dimethylcyclohexanol with palmitic acid, and distillation of the ester at 340–350°. It had b. p. 124–125° (Found: C, 87.1; H, 12.7. Calc. for C_8H_{14} : C, 87.3; H, 12.7%). In order to ensure that no movement of the double bond had taken place, the hydrocarbon was oxidised with potassium permanganate in acetone, and the resulting acid gave β -methyladipic dianilide, m. p. 198° (Found: C, 73.0; H, 7.2. Calc. for $C_{19}H_{22}O_2N_2$: C, 73.5; H, 7.1%). Markownikoff (*J. Russ. Phys. Chem. Soc.*, 1903, **35**, 226) gives m. p. 197–198°. Addition of nitrosyl chloride gave a solid which was refluxed with sodium acetate in acetic acid and hydrolysed with dilute mineral acid to a ketone, b. p. 93–96°/16 mm. (cf. Wallach, *Annalen*, 1913, **395**, 275; **397**, 198). This gave rise to a 2:4-dinitrophenylhydrazone as bright red needles (from ethyl acetate-alcohol), m. p. 183–184° (Found: C, 55.0; H, 5.4. $C_{14}H_{18}O_4N_4$ requires C, 55.3; H, 5.3%), which must be derived from 2:4-dimethylcyclohex-2-enone, since it is not identical with the derivatives from 2:6-dimethyl-, m. p. 153°, from 3:5-dimethyl-, m. p. 165°, or from 4:6-dimethylcyclohex-2-enone, m. p. 164–165°. The semicarbazone had m. p. 167–168° (Found: C, 59.5; H, 8.3. Calc. for $C_8H_{14}ON_3$: C, 59.7; H, 8.3%). This examination was necessary, since Wallach (*loc. cit.*) gives m. p. 130–131° for the nitropiperidine and m. p. 194–195° for the semicarbazone obtained as above.

Methylallyl butyl ether, obtained from sodium *n*-butoxide and methylallyl chloride, b. p. 135–137°, n_D^{20} 1.3942, gave 1-butoxy-2-methylpropene, b. p. 138–140°, n_D^{20} 1.4230 (Found: C, 75.0; H, 12.6. $C_8H_{16}O$ requires C, 75.0; H, 12.5%), which, unlike the starting material, gave the 2:4-dinitrophenylhydrazone of isobutaldehyde on boiling with Brady's reagent, m. p. 182° (Found: C, 47.6; H, 4.8. Calc. for $C_{10}H_{18}O_4N_4$: C, 47.4; H, 5.1%). Mathiessen and Hagedorn (*Mikrochem.*, 1941, **29**, 58) give m. p. 183.5–185°.

3-Methoxycyclohexene (Berlande, *Bull. Soc. chim.*, 1942, **9**, 653) gave a hydrocarbon, b. p. 78–82°, n_D^{20} 1.4720 (Found: C, 89.6; H, 10.4. Calc. for C_8H_{12} : C, 90.0; H, 10.0%). It was unsaturated, but did not react with maleic anhydride and was probably a mixture of cyclohexene and benzene. A small higher-boiling fraction contained no 1-methoxycyclohexene since it failed to react with Brady's reagent.

Action of Sodium or Potassium Amide on Unsaturated Hydrocarbons.—The metal (2 g.) in ammonia (100 c.c.) was converted into the amide by the catalytic action of ferric nitrate, the hydrocarbon (10 g.) added, and the mixture stirred for 6 hours with exclusion of air. The product was worked up by addition of ice and ether extraction; in many cases considerable loss of material occurred by volatilisation.

2:5-Dihydrotoluene was obtained by reduction of toluene with sodium and alcohol in liquid ammonia (cf. dihydro-*m*-xylene, Part III); b. p. 114–115°, n_D^{20} 1.4695 (Found: C, 89.2; H, 10.7. C_8H_{10} requires C, 89.4; H, 10.6%), nitropiperidine m. p. 122–123°. It gave rise to a product, b. p. 108–110°, n_D^{20} 1.4890 (Found: C, 90.4; H, 9.3. Calc. for C_7H_8 : C, 91.3; H, 8.7%. Calc. for C_7H_{12} : C, 87.5; H, 12.5%). This gave a small yield of the nitropiperidine, m. p. 146–147°, of 1-methylcyclohexene, and must consist of an admixture of a trace of this with toluene. After treatment of 2:5-dihydrotoluene with sodium amide in ammonia for one hour the product (b. p. 108–112°) was left with maleic anhydride in cold acetone for 5 hours and then steam-distilled. The small residue crystallised and the adduct was recrystallised from aqueous methanol; m. p. 62–63° (Found: C, 68.5; H, 6.2. $C_{11}H_{12}O_3$ requires C, 68.8; H, 6.2%). Brief heating on the steam-bath with *p*-toluidine gave a derivative, m. p. 182° (from alcohol) (Found: C, 77.2; H, 6.7. $C_{18}H_{18}O_2N$ requires C, 76.8; H, 6.7%). For comparison the derivative of 1-methylcyclohexa-1:5-diene was synthesised from cyclohex-2-enone by the action of methylmagnesium iodide, dehydration of the carbinol by distillation with a trace of iodine, and treatment

of the product (b. p. 110°) with maleic anhydride in cold acetone. The adduct, b. p. 180°/16 mm., solidified in ice and melted at about 14° (Found: C, 68.8; H, 6.0. $C_{11}H_{18}O_2$ requires C, 68.7; H, 6.2%). The derivative obtained with *p*-toluidine had m. p. 175° (from alcohol), depressed by the above (Found: C, 76.4; H, 6.9. $C_{11}H_{18}O_2N$ requires C, 76.8; H, 6.7%).

2:5-Dihydro-*m*-xylene (Part I) gave *m*-xylene, b. p. 136–138°, n_D^{18} 1.4960, and no conjugated material could be detected.

4:5-Dihydro-*m*-xylene, b. p. 135°, was obtained by the action of methylmagnesium iodide on 3-methylcyclohex-2-enone followed by dehydration of the carbinol by distillation with a trace of iodine. It gave rise to a colourless oil, b. p. 135–137° (Found: C, 90.2; H, 9.7. Calc. for C_9H_{16} : C, 90.5; H, 9.5%). The ultra-violet absorption of this was consistent with its being a mixture of 80% of *m*-xylene and 20% of starting material.

Oct-1-ene was prepared by the action of amylmagnesium bromide on allyl bromide (cf. Henne, Chanan, and Turk, *J. Amer. Chem. Soc.*, 1941, **63**, 3474); b. p. 119°. It gave rise to a product, b. p. 119–122°, which was shown by its infra-red absorption spectrum to contain 80% of oct-1-ene and 20% of an isomer, probably oct-2-ene.

2:5-Dimethylhexa-1:5-diene (*idem, ibid.*), b. p. 114°, n_D^{18} 1.4360, gave rise to 2:5-dimethylhexa-2:4-diene, b. p. 133–135°, n_D^{18} 1.4780, m. p. 13°. Henne and Turk (*J. Amer. Chem. Soc.*, 1942, **64**, 826) give for this substance b. p. 134.5°, n_D^{20} 1.4781, m. p. 14°.

4-Phenylbut-1-ene (obtained by the action of benzylmagnesium chloride on allyl bromide) when treated as above gave the red colour but the product was largely high-boiling, probably produced by the polymerisation of phenylbut-1-ene. By limiting the reaction time to 2 hours some polymer was formed together with a product, b. p. 175–182° (Found: C-Me, 7.3. Calc. for $C_9H_9CH_3$: C-Me, 11.4%). From the b. p. it was probably a mixture containing a considerable proportion of phenylbut-2-ene.

Methylgeraniolene, b. p. 167°; *d*-limonene, b. p. 175°, n_D^{20} + 73.5°; *d*-sylvestrene, b. p. 173.5°, n_D^{20} + 17°; and 1:2:3:4:1':2':3':4'-octahydrotetraphenyl (Berlande, *loc. cit.*), b. p. 232–235° (used in ether, 50 c.c., because of its low solubility in ammonia), were all recovered unchanged, the product from the last substance failing to show any reaction with maleic anhydride, and the optical rotations of the active compounds were unchanged. 1:3- and 2:4-Dimethylcyclohexene gave their characteristic nitroloperidines after treatment, and 4-methylcyclohexene showed unaltered infra-red absorption.

Reduction of Hydrocarbons.—2:5-Dihydrotoluene (10 g.) and sodium (5 g.) in ammonia (100 c.c.) after 4 hours gave a product, b. p. 105–110°, n_D^{18} 1.4731 (Found: C, 89.4; H, 10.4%), shown by its infra-red absorption to contain 40% of toluene, 50% of 1-methylcyclohexene, and 10% of 3-methylcyclohexene.

2:5-Dihydrotoluene (10 g.) with calcium hexamine (from the metal, 10 g.) over 48 hours gave a product, b. p. 104–108°, n_D^{20} 1.4470 (Found: C, 87.3; H, 12.3. Calc. for C_7H_{12} : C, 87.5; H, 12.5%), which contained about 80% of 1- and 20% of 3-methylcyclohexene (infra-red absorption). Reduction of toluene by the same method gave a product still containing aromatic material, and the process was repeated on this using the hexamine from calcium (5 g.) and a mixture identical with the above obtained (infra-red absorption).

4:5-Dihydro-*m*-xylene (3.5 g.) was reduced with sodium (2 g.) and alcohol (4 g.) in ammonia (45 c.c.), giving a product, b. p. 124–126° (Found: C, 86.8; H, 12.3. Calc. for C_9H_{14} : C, 87.3; H, 12.7%). That it was chiefly 1:3-dimethylcyclohexene was shown by the preparation of the nitroloperidine, m. p. 156–157°. For comparison, the hydrocarbon was prepared by distilling the palmitate of 2:6-dimethylcyclohexanol at 330–350°; b. p. 125–126° (Found: C, 87.2; H, 12.7. Calc. for C_9H_{14} : C, 87.3; H, 12.7%). This gave the nitroloperidine, m. p. 156–157°, also obtained from the reduction products of *m*-xylene and 2:5-dihydro-*m*-xylene (Part III, *loc. cit.*). Removal of hydrogen chloride from the nitroschloride by means of sodium acetate in boiling acetic acid (cf. Wallach, *loc. cit.*) and treatment of the resulting oxime with Brady's reagent gave the derivative of 2:6-dimethylcyclohex-2-enone, m. p. 153°, already obtained from the reduction product of 2:6-dimethylanisole (Part I, *loc. cit.*), thus confirming the position of the double bond in the hydrocarbon. Dehydration of 2:6-dimethylcyclohexanol with acid reagents such as phosphoric oxide produced considerable isomerisation to give 2:4-dimethylcyclohexene.

4-Phenylbut-1-ene (10 g.) and sodium (5 g.) in liquid ammonia (100 c.c.) were left for 5 hours, excess of sodium destroyed with ammonium chloride, and the product worked up as usual. Distillation gave an oil, b. p. 177–182°, which was shaken with ice-cold aqueous potassium permanganate until a permanent colour was obtained. The distilled oil (4 g.) was phenylbutane, b. p. 179–181° (Found: C, 90.3; H, 10.1. Calc. for $C_{10}H_{14}$: C, 89.6; H, 10.4%).

1:3-Dimethyl- and 2:4-dimethylcyclohexene, *d*-limonene, and *d*-sylvestrene were unchanged by sodium in ammonia or by calcium hexamine, as shown by unchanged physical constants, in particular the optical rotations of the last two substances. Methylgeraniolene and 4-methylcyclohexene were also shown by means of their infra-red absorption to be unchanged.

2-Ethoxy-3:4-dihydronaphthalene (kindly presented by Mr. C. T. Beer), reduced with sodium (4 equivs.) and ammonia either in presence or in absence of alcohol (5 equivs.), gave a hydrocarbon as the product. Obtained in presence of alcohol, this showed slight unsaturation to bromine, but with sodium alone it was 1:2:3:4-tetrahydronaphthalene, b. p. 202–208° (Found: C, 90.6; H, 9.3. Calc. for $C_{10}H_{12}$: C, 90.9; H, 9.1%). When only 2 equivs. of sodium were employed the product was a mixture of about equal parts of tetralin and starting material.

The author wishes to express his gratitude to Dr. D. H. Whiffen and Dr. R. E. Richards for measuring and interpreting the infra-red spectra, and to Dr. F. B. Strauss for the ultra-violet spectrum measurements, which were carried out in alcohol.

This work was carried out during the tenure of an I.C.I. Research Fellowship.

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[Received, February 18th, 1947.]

328. Cinnolines. Part XIV. N-Oxides of 4-Arylcinnolines. Conversion of 4-Substituted Cinnolines into Indoles.

By C. M. ATKINSON and J. C. E. SIMPSON.

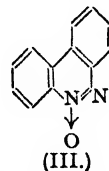
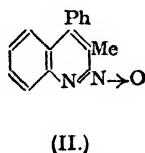
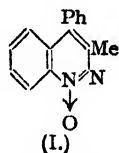
Treatment of 4-arylcinnolines with hydrogen peroxide in acetic acid gives the corresponding N-oxides. In contrast to 3:4-benzocinnoline N-oxide (III) (King and King, *J.*, 1945, 824), 4-phenyl-3-methylcinnoline N-oxide (I) is not nitrated selectively, four isomeric mono-nitro-derivatives being obtained.

Alkaline reduction of 4-substituted cinnolines leads to formation of the corresponding indoles; with 6- and 7-chloro-3-methylcinnoline reductive dehalogenation also occurs, and skatole is produced.

ALTHOUGH formally comparable cinnolines, quinolines, and quinazolines have certain reactions in common, this is not always so (cf. Schofield and Simpson, *J.*, 1946, 472; Simpson, *J.* 1946, 1035; and unpublished work), and in attempting to account for the properties of certain types of cinnoline derivatives, the following * experiments were carried out to examine the possibility that this heterocyclic group might retain some of the characteristics of azo-compounds.

In the first place, we have found that 4-arylcinnolines are readily converted into N-oxides on treatment with hydrogen peroxide in acetic acid. This reaction was tried with 4-phenyl-3-methyl-, 4-phenyl-3-benzyl-, 3-phenyl-4-*p*-anisyl-, 4-*p*-anisyl-3-methyl-, and 3:4-diphenylcinnoline, and in each case the corresponding N-oxide was isolated in good yield. This result was not of direct diagnostic value, for although the oxidation of azo- to azoxy-compounds can be effected under somewhat similar conditions (*Chem. Reviews*, 1931, 9, 126), the formation of N-oxides is likewise characteristic of many heterocyclic types, *e.g.*, pyridines and quinolines (Meisenheimer, *Ber.*, 1926, 59, 1848), phenanthrolines (Linsker and Evans, *J. Amer. Chem. Soc.*, 1946, 68, 403), and quinoxalines (McIlwain, *J.*, 1943, 322; Linsker and Evans, *loc. cit.*, and *p.* 874), although the cinnoline N-oxides, in contrast to the quinoxaline derivatives (McIlwain, *loc. cit.*), showed complete absence of peroxidic properties.

Our experiments with 4-methylcinnolines (this vol., *p.* 808) and with certain N-alkylcinnolinium salts (following paper) have indicated that the cinnoline N-oxides should be formulated as (I) and not as (II). If (I) is properly regarded as a vinylogue of an azoxy-compound, it should undergo preferential substitution in the 4-phenyl group. The nitration of (I) was therefore examined, but proved to be unexpectedly complex, and gave rise to four isomers, designated α -, β -, γ -, and δ -nitro-4-phenyl-3-methylcinnoline N-oxide; there was no evidence of the formation of dinitro-compounds.



No definite conclusion regarding the azoxy-compound-like nature of 4-arylcinnoline N-oxides can be drawn from these results, but the complete lack of any selective attack on the molecule was unexpected, and is in marked contrast to the results of King and King (*J.*, 1945, 824) which appeared after the present work had been discontinued. These workers investigated the nitration of 3:4-benzocinnoline N-oxide (III), and, arguing from essentially the same premises as ourselves, anticipated and encountered nitration almost exclusively in one position, which was assumed to be in the ring remote from the N-oxide linkage.

As an alternative approach to the discovery of azo-compound characteristics in 4-substituted cinnolines, we turned our attention to the reduction of such compounds with sodium and alcohol. 4-Phenyl-3-methylcinnoline gave a mixture of unchanged material (1 part) and 3-phenyl-2-methylindole (2.5 parts), and when the reaction was extended to other compounds it was evident that indole formation, accompanied by evolution of ammonia, is the predominating reaction. The results are summarised in the following table, in which the figures (representing ammonia values expressed as percentages of the amounts corresponding to complete conversion into indole) indicate the extent of the reaction. Examination of the products of reduction gave the following results. From (i) only the indole was isolated. In experiments (ii) and (vi) both the indole and unchanged material were identified. Experiment (v) gave an oil,

* It has been necessary temporarily to discontinue our study of 4-arylcinnolines, and the experiments with such compounds recorded in this and the following paper are therefore incomplete.

(iii) gave an unidentified mixture, and (iv) gave an oil together with unchanged cinnoline. Skatole and 4-methylcinnoline were obtained from (vii) and also from (ix), and (viii) yielded skatole and (as picrate) a substance which was not identical with the picrate of 4-methylcinnoline or of its 6- and 7-chloro-derivatives.

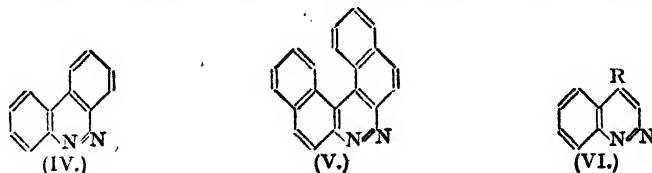
Cinnoline.	NH ₃ evolved, %.	Cinnoline.	NH ₃ evolved, %.
(i) 4- <i>p</i> -Anisyl-3-methyl-	58	(vi) 4- <i>p</i> -Hydroxyphenyl-	53
(ii) 4- <i>p</i> -Hydroxyphenyl-3-methyl- ...	55	(vii) 4-Methyl-	65
(iii) 3-Phenyl-4- <i>p</i> -anisyl-	3	(viii) 6-Chloro-4-methyl-	57
(iv) 3-Phenyl-4- <i>p</i> -hydroxyphenyl- ...	1	(ix) 7-Chloro-4-methyl-	60
(v) 4- <i>p</i> -Anisyl-	15		

The production of 3-methylindole from each of the 4-methylcinnolines is noteworthy. It is possible that the chloro-indole may be formed and may then undergo further reduction, but the results of (ix) indicate that, in this case at least, dehalogenation of the cinnoline occurs more readily than ring-contraction. The unidentified picrate from (viii) might well be that of 5-chloro-3-methylindole, but owing to interruption of the work it has not been possible to investigate this point.

The *indoles* obtained from (i), (ii), and (vi) are apparently new compounds, and their orientation is based on the assumption (which appears to be justified by the formation of skatole and 3-phenyl-2-methylindole) that the ring-contraction is not accompanied by any form of molecular rearrangement.

A comparison of (i) with (v) and of (v) with (vi) suggests that a 3-methyl group and a *p*-hydroxyl group (in the 4-phenyl substituent) both favour the reaction as compared with hydrogen and a methoxyl group respectively; a 3-phenyl group, on the other hand, has a strongly inhibitory effect in conjunction with a 4-aryl group. The contrast between (v) and (vi—ix) seems to indicate that the normal electromeric effect of the 4-substituent is not the sole controlling influence, and it is possible that chemical and spatial factors are both involved. This conclusion is supported by the following evidence from the literature, which, taken in conjunction with our own results, indicates that the tendency of cinnolines to pass into indoles is markedly dependent on the nature and degree of substitution in the pyridazine ring.

(a) Neber, Knöller, Herbst, and Trissler (*Annalen*, 1929, 471, 113), working with various acid reducing media, found that 4-phenylcinnoline yielded 3-phenylindole *via* 4-phenyl-1:2-dihydrocinnoline, and that oxindole was formed from 3-hydroxycinnoline; no indoxyl or indigo derivative resulted, however, from 4-hydroxycinnoline, which (with hydriodic acid and red phosphorus) gave 4-hydroxytetrahydrocinnoline hydriodide. (b) 3:4-Benzocinnolines of type (IV) are more stable, as they are themselves produced from 2:2'-dinitrodiaryls by reduction in alkaline or acid media or electrolytically (Täuber, *Ber.*, 1891, 24, 3081; Meyer, *ibid.*, 1893, 26, 2238; Ullmann and Dieterle, *ibid.*, 1904, 37, 23), and 5:6-benzo-1':2':4:3-naphthocinnoline (V) is also formed in an alkaline reducing medium (from β -nitronaphthalene; Meisenheimer and Witte, *Ber.*, 1903, 36, 4153). (c) If it is assumed that the ammonia evolved in the cinnoline \rightarrow indole reaction is formed by ring-closure of an intermediate diamine, then



a comparable variation in stability may also be discerned among the diamines corresponding to types (VI), (IV), and (V). Thus the diamines derived from a 4-substituted cinnoline (VI; R = Ar or Me) do not survive the reaction conditions used (sodium and alcohol), but they have been isolated from compounds of type (IV) (King and King, *loc. cit.*) and from (V) (Meisenheimer and Witte, *loc. cit.*). (d) Formation of the pyridazine ring [regeneration of type (IV)] from 2:2'-diaminodiaryls occurs at least as readily (Täuber, *Ber.*, 1893, 26, 1703; 1896, 29, 2270; Dobbie, Fox, and Gauge, *J.*, 1911, 1615; Sandin and Cairns, *J. Amer. Chem. Soc.*, 1936, 58, 2016) as does the conversion of such compounds into carbazoles (formation of the pyrrole ring) (Täuber, *loc. cit.*; Meisenheimer and Witte, *loc. cit.*; Dobbie, Fox, and Gauge, *loc. cit.*; King and King, *loc. cit.*). Such variations in stability of the diamines are presumably an indication of the greater degree of ring-strain involved in the carbazole, as compared with the indole, nucleus.

EXPERIMENTAL.

(Melting points are uncorrected.)

4-*p*-Hydroxyphenyl-3-methylcinnoline.—4-*p*-Anisyl-3-methylcinnoline (5 g.; *J.*, 1946, 673) was refluxed with hydrobromic acid (37 c.c., *d* 1.5) for 1 hour. The cold mixture was basified (ammonia), the supernatant liquid decanted, and the solid dissolved in aqueous sodium hydroxide, and the combined alkaline solutions were made acid with acetic acid. 4-*p*-Hydroxyphenyl-3-methylcinnoline (yield of almost pure compound, 4.4 g.) separated from alcohol in small yellow prisms, m. p. 241–242° (Found: N, 12.2. $C_{13}H_{11}ON_2$ requires N, 11.9%); its solution in warm 2*N*-sodium hydroxide deposited silky needles of the sodium salt on cooling.

4-*p*-Hydroxyphenylcinnoline.—4-*p*-Anisylcinnoline was prepared by the method of Stoermer and Gaus (*Ber.*, 1912, 45, 3104), but as a result of its poor crystallising properties was difficult to purify and was most conveniently handled as the hydrochloride, which crystallised well from acetic acid or 2*N*-hydrochloric acid in bright yellow needles, m. p. 215–217° (decomp.) after shrinking at 195°. The salt (15 g.) was refluxed for 1 hour with hydrobromic acid (105 c.c., *d* 1.45) and the crude hydroxyphenylcinnoline isolated as described above. It was best purified by way of the *acetoxy*-compound [obtained by refluxing the crude base with acetic anhydride (5 parts) for $\frac{1}{2}$ hour], which separated from aqueous alcohol in pale yellow rectangles, m. p. 127.5–128° (Found: C, 72.35; H, 4.8; N, 11.35. $C_{16}H_{13}O_2N_2$ requires C, 72.7; H, 4.6; N, 10.6%), and when boiled with 5*N*-hydrochloric acid was rapidly hydrolysed with quantitative separation of 4-*p*-hydroxyphenylcinnoline hydrochloride, m. p. 270–273° (decomp.); this when boiled with water gave the free base as yellow prisms (from alcohol), m. p. 234–235° (Stoermer and Gaus, *loc. cit.*, give m. p. 230°).

3-Phenyl-4-*p*-hydroxyphenylcinnoline.—3-Phenyl-4-*p*-anisylcinnoline (5.5 g.; *J.*, 1946, 673) was refluxed with hydrobromic acid (55 c.c., *d* 1.5) and acetic acid (27.5 c.c.) for 2½ hours; the mixture was cooled, basified with ammonia, and the base recrystallised from acetic acid. 3-Phenyl-4-*p*-hydroxyphenylcinnoline (yield of almost pure compound, 4.9 g.) formed almost colourless needles (occasionally thin parallelepipeds), m. p. 283–286° (Found: C, 80.3; H, 4.9. $C_{20}H_{14}ON_2$ requires C, 80.5; H, 4.7%).

Preparation of Cinnoline N-Oxides.—The cinnolines (1 part) were dissolved in glacial acetic acid (8–10 parts), hydrogen peroxide (5–8 parts, 30%) added, and the clear solutions heated at 90–95° for 2 hours; the products separated on cooling and, if necessary, dilution with water (yields, 80–90%). 4-Phenyl-3-methylcinnoline N-oxide formed long straw-coloured needles, m. p. 124–125°, from aqueous alcohol or aqueous acetic acid (Found: C, 75.85; H, 5.2; N, 12.0. $C_{15}H_{11}ON_2$ requires C, 76.25; H, 5.1; N, 11.9%). 4-Phenyl-3-benzylcinnoline N-oxide, colourless needles from aqueous alcohol, had m. p. 110–111° to a turbid melt which cleared at 130° (Found: C, 80.4; H, 4.8; N, 9.4. $C_{21}H_{16}ON_2$ requires C, 80.7; H, 5.2; N, 9.0%). 3:4-Diphenylcinnoline N-oxide formed radial clusters of stout yellow prismatic needles, m. p. 196–198° (clear at 202°), from ethyl acetate or acetic acid, and was very sparingly soluble in alcohol (Found: C, 80.4; H, 4.65; N, 9.5. $C_{20}H_{14}ON_2$ requires C, 80.5; H, 4.7; N, 9.4%). 4-*p*-Anisyl-3-methylcinnoline N-oxide separated from aqueous acetic acid in colourless blades, m. p. 161° (Found: C, 71.9; H, 5.0. $C_{16}H_{11}O_2N_2$ requires C, 72.1; H, 5.3%). 3-Phenyl-4-*p*-anisylcinnoline N-oxide, light brown blades from aqueous alcohol, had m. p. 176–177° (Found: C, 77.1; H, 4.85. $C_{21}H_{16}O_2N_2$ requires C, 76.8; H, 4.9%).

Nitration of 4-Phenyl-3-methylcinnoline N-Oxide.—The substance (1.5 g.) was added during 35 minutes to 9 c.c. of a mixture of nitric acid (10.5 c.c., *d* 1.48) and sulphuric acid (3 c.c., *d* 1.84). After a total of 1½ hours (reaction temperature –13° to –10° throughout the experiment) the solution was poured into water and the precipitated solid filtered off, washed, and digested with alcohol (1.55 g., m. p. ca. 160–175°). Material so obtained, representing 2.5 g. of cinnoline oxide, was digested with acetone, and the insoluble fraction repeatedly crystallised from a large volume of this solvent; α -nitro-4-phenyl-3-methylcinnoline N-oxide was thus obtained in faintly yellow, microcrystalline nodules, m. p. 256–257° (Found: C, 64.0; H, 3.95; N, 15.2. $C_{16}H_{11}O_3N_2$ requires C, 64.0; H, 3.95; N, 14.9%). This compound was very much less soluble in acetone than the isomers described below; it was insoluble in hot aqueous sodium hydroxide and in 2*N*-hydrochloric acid, and sparingly soluble in hot 6*N*-hydrochloric acid.

Attempted fractional crystallisation (from benzene and acetone) of the material in the acetone filtrates from the α -compound gave only a little impure β -compound. A benzene solution (200 c.c.) of the combined fractions was drawn through a 26 cm. column of Merck's alumina (50 g.) prepared with benzene (80 c.c.). The filtrate and successive washings (50 c.c. portions of benzene) were separately evaporated, yielding respectively (a) 80 mg., (b) 530 mg., (c) 530 mg., (d) 290 mg., (e) 140 mg., and (f) 80 mg. Fractions (a) and (b) were solid, (c) and (d) semi-crystalline, and (e) and (f) were brown resins.

A solution of fraction (b) in acetone, after removal of a little impure α -compound, gave a product which, after repeated crystallisation from acetone and finally from ethyl acetate, yielded the β -isomer as pale yellow, brittle, hexagonal plates, m. p. 235–238° after previous shrinking (Found: C, 63.7; H, 3.75; N, 15.05%).

Fraction (c) was similarly freed from a little α -compound; recrystallisation (finally from slightly aqueous acetone) furnished small, soft, lemon-yellow prismatic needles, m. p. 218–219° (clear at 222°) of the γ -isomer; a mixture with the β -compound had m. p. 200–220° (Found: C, 63.95; H, 3.95; N, 15.0%). From the filtrates a small amount of the β -compound was isolated by means of ethyl acetate.

Fraction (d) (extremely soluble in acetone) was combined with the material remaining in the mother-liquors of fractions (b) and (c), and the whole fractionated from ethyl acetate; some β -isomer was first removed, and the filtrates then deposited δ -nitro-4-phenyl-3-methylcinnoline N-oxide, which separated in rosettes of small colourless needles, m. p. 198–199° (180–188° when mixed with the γ -compound) (Found: C, 64.0; H, 3.8; N, 15.25%).

Owing to the difficulty of separation, it was not possible to assess the relative proportions in which the isomers were present in the crude nitration product.

Reduction of 4-Substituted Cinnolines.—(a) A solution of 4-phenyl-3-methylcinnoline (2.5 g.) in

alcohol (100 c.c.) was reduced, and the product isolated, as described in (b). The oil obtained by evaporation of the washed and dried extract was treated (in alcohol; 20 c.c.) with picric acid (2.5 g.), and the mixture of picrates (3.75 g.) fractionated from alcohol. The least soluble fraction was 4-phenyl-3-methylcinnoline picrate (1 g.), which formed small brown leaflets or prismatic needles, m. p. 179—181° alone and mixed with an authentic specimen (m. p. 180—181°) (Found: C, 55.85; H, 3.4; N, 15.6. $C_{11}H_{13}N_2C_6H_5O_7$ requires C, 56.1; H, 3.35; N, 15.6%). The filtrates yielded 3-phenyl-2-methylindole picrate (2.5 g.) as purple needles with a green reflex, m. p. 139—141° (Found: C, 58.0; H, 3.85; N, 13.15. Calc. for $C_{11}H_{13}N_2C_6H_5O_7$: C, 57.8; H, 3.7; N, 12.8%) (Trenkler, *Annalen*, 1888, 248, 106, gives m. p. 141—142°).

(b) 4-*p*-Anisyl-3-methylcinnoline (0.01 mol.) in alcohol (150 c.c.) was refluxed and treated with sodium (10 g., ca. 20 pieces) during $\frac{1}{2}$ hour, added through a trap to avoid loss of the evolved gases, which were led *via* the reflux condenser into two flasks containing *N*/5-hydrochloric acid. After the sodium had dissolved the system was swept out with a slow stream of nitrogen for $\frac{1}{2}$ hour; the mixture was then poured into water (400 c.c.) and extracted with ether. [This procedure was followed in all the experiments described below, and in general at least two runs were carried out for each compound; individual results, of which the ammonia figures on p. 1650 are mean values, agreed within 5—6%. In experiments with cinnolines containing a *p*-hydroxyphenyl group, the alkaline solution from the ether-extraction was acidified to pH 8 with acetic acid and again extracted (such extracts are referred to as "pH 8 fractions"). Separation of the reaction products was only qualitative.] The extract yielded 3-*p*-anisyl-2-methylindole as sole crystalline product, separating from benzene-ligroin (b. p. 40—60°) or from aqueous alcohol in colourless needles, m. p. 127—128° (Found: C, 80.8; H, 6.25. $C_{11}H_{13}ON$ requires C, 81.0; H, 6.3%). The picrate, prepared in benzene solution, formed almost black, lustrous needles, m. p. 128—130° (Found: C, 56.65; H, 3.95; N, 12.3. $C_{11}H_{13}ON.C_6H_5O_7N_3$ requires C, 56.65; H, 3.85; N, 12.0%).

(c) 4-*p*-Hydroxyphenyl-3-methylcinnoline gave an aqueous alkaline solution which, after ether-extraction, deposited a solid which did not melt at 330° (evidently the sodium salt of the cinnoline). The ether-extract yielded 3-*p*-hydroxyphenyl-2-methylindole, which crystallised from benzene in almost colourless prisms, m. p. 135—136° (Found: C, 80.2; H, 5.8; N, 7.0. $C_{11}H_{13}ON$ requires C, 80.7; H, 5.9; N, 6.3%), soluble in cold 2*N*-sodium hydroxide, but not in aqueous ammonia or sodium carbonate. The pH 8 fraction was an oil which (in alcohol) gave unreduced cinnoline, m. p. 238—241° (identified by mixed m. p.).

(d) 3-Phenyl-4-*p*-anisylcinnoline gave a crystalline mixture, m. p. 47—70°. Digestion with ether afforded, with heavy losses, a less soluble fraction, m. p. 132—145° (unchanged by recrystallisation from alcohol), which was not further purified.

(e) The extract of the alkaline mixture from the reduction of 3-phenyl-4-*p*-hydroxyphenylcinnoline and also the pH 8 fraction yielded unchanged material, m. p. and mixed m. p. 283—286°, but unidentified products were also present.

(f) 4-*p*-Anisylcinnoline gave a glassy resin which could not be obtained crystalline or converted into a crystalline picrate or hydrochloride.

(g) By extraction of the alkaline solution, 4-*p*-hydroxyphenylcinnoline yielded 3-*p*-hydroxyphenylindole, which crystallised from benzene in small golden prismatic needles, m. p. 152—154° (Found: C, 79.75; H, 5.2; N, 6.8. $C_{11}H_{11}ON$ requires C, 80.35; H, 5.3; N, 6.7%); the solubility of this substance in alkalis was similar to that of its homologue described in (c). The pH 8 fraction was an oily solid from which 4-*p*-hydroxyphenylcinnoline was isolated (m. p. 234—235° alone and mixed with an authentic specimen).

(h) The ether extract from the reduction of 4-methylcinnoline gave an oily solid which on recrystallisation from ligroin (b. p. 40—60°) yielded skatole, m. p. 95.5—96.5° (Found: C, 82.0; H, 7.5; N, 10.6. Calc. for C_9H_9N : C, 82.4; H, 6.9; N, 10.7%). The ligroin filtrates were evaporated, and the residue was treated with picric acid in benzene and the resultant solid recrystallised from alcohol, from which 4-methylcinnoline picrate separated in dark green prismatic needles, m. p. 177—178° alone and mixed with an authentic specimen (this vol., p. 811).

(i) In the case of 7-chloro-4-methylcinnoline, skatole separated directly when the mixture was poured into water, and was collected and identified (m. p. 96.5° alone and when mixed with the sample described above). The picrate, soft red needles from alcohol, had m. p. 177—178° (Marion and Ashford, *Canad. J. Res.*, 1945, 23, B, 26, give m. p. 182°) (Found: C, 50.0; H, 3.4. Calc. for $C_9H_8N.C_6H_5O_7N_3$: C, 50.0; H, 3.4%). It turned yellow on standing in the air, and after 3 days had m. p. 225—230°. The aqueous filtrate from the skatole was extracted with ether, yielding an oil from which 4-methylcinnoline was isolated as picrate (m. p. 170—173°, not depressed when mixed with authentic material).

(j) Ether-extraction of the product from 6-chloro-4-methylcinnoline gave an oil, from which skatole (m. p. 95—96°) was isolated by means of ligroin (b. p. 40—60°) (picrate, m. p. 172—174°, not depressed by admixture with the specimen described above). The first ligroin filtrate was evaporated and the residue converted into the picrate, which was digested with alcohol; the green solid so obtained had m. p. 185—187° (6-chloro-4-methylcinnoline picrate has m. p. 154—156°; this vol., p. 811) and gave marked depressions in m. p. when mixed with the picrates of skatole and 4-methylcinnoline.

We are indebted to Imperial Chemical Industries Limited (Dyestuffs Division) for support of this work, and to the Council of the Durham Colleges for a grant from the Research Fund during the early stages.

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[Received, February 18th, 1947.]

329. Cinnolines. Part XV. The Alkaline Decomposition of Some Quaternary Salts of 4-Substituted Cinnolines.

By J. C. E. SIMPSON.

The reaction which occurs when 4-substituted alkylcinnolinium salts are treated with alkali depends markedly on the nature of the 4-substituent. 4-*p*-Hydroxyphenylcinnoline ethiodide gives, as major products, acetaldehyde and the parent base, and the reaction shows significant qualitative similarities to that previously studied (McIlwain, *J.*, 1937, 1704) with alkylphenazonium salts. On the other hand, retention of the *N*-alkyl group is observed with 6-chloro-4-aminocinnoline methiodide, which yields mainly ammonia and 6-chloro-1-methyl-4-cinnolone.

THE experiments described in this paper were undertaken with the object of locating the basic centre of 4-substituted cinnolines, the scheme envisaged being the preparation of quaternary salts of such compounds and study of their decomposition reactions in the hope that the point of quaternary salt formation, and hence the basic centre, might thus be disclosed. Combination of 4-phenyl-3-methyl-, 4-*p*-hydroxyphenyl-, and 3-phenyl-4-*p*-hydroxyphenylcinnoline with ethyl iodide proceeded readily, giving the corresponding ethiodides in reasonably high yields. Preliminary experiments showed that 4-*p*-hydroxyphenylcinnoline ethiodide (I; R = H) was very readily decomposed under mild alkaline conditions; an intense crimson coloration was first produced, and the parent cinnoline was isolated from the reaction mixture. Although this result was disappointing from the point of view of the objective mentioned, the reaction seemed of sufficient interest to merit further study. It was then found that the decomposition was not alkali-catalysed, that it could be effected by cold or hot aqueous sodium hydroxide or carbonate and by hot ammonium hydroxide, and that acetaldehyde was a major product of the reaction.

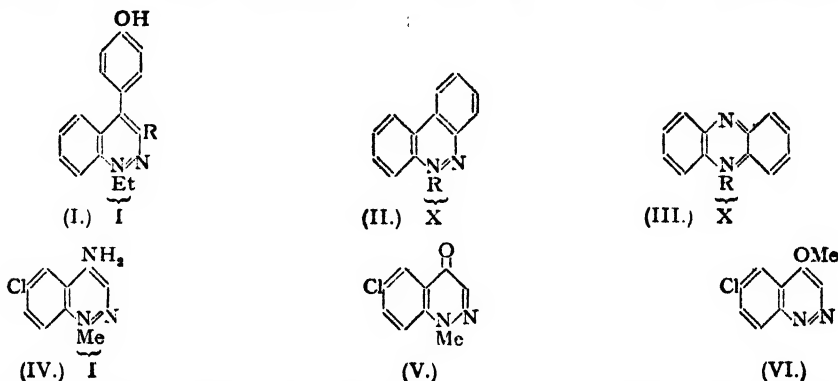
The decomposition of 3-phenyl-4-*p*-hydroxyphenylcinnoline ethiodide (I; R = Ph) was not examined in detail, but probably proceeds analogously, as the parent base was readily isolated, and the smell of acetaldehyde was noticeable during the reaction. It is possible that quaternary salts of 3:4-benzocinnoline (II) decompose in the same way, as Ullmann and Dieterle (*Ber.*, 1904, 37, 23) noted that the parent base was regenerated by treatment of such salts with alkali, but did not investigate the reaction further. This type of reaction is strongly reminiscent of that shown by phenazonium salts (III) in alkaline solution; the regeneration of the parent base from such salts has been observed by various workers, and a more recent study of this reaction by McIlwain (*J.*, 1937, 1704) has shown that it takes the course $2 \text{ BMc} \cdot \text{OH} \longrightarrow \text{B} + \text{BHMc} + \text{CH}_2\text{O} + \text{H}_2\text{O}$.

There is thus a striking parallel between the decomposition of alkylphenazonium salts and that of certain alkylcinnolinium halides. However, further examination of the decomposition of (I; R = H) disclosed that the yield both of 4-arylcinnoline and of acetaldehyde was 70–75 mols.% (based on quaternary salt) and thus indicated that the relationship between the reactions is merely qualitative. The extent to which the 25% of unrecovered cinnoline functions as hydrogen acceptor is unknown; identification of hydrogen as a product of reaction was not attempted, and the non-volatile residue, after removal of 4-*p*-hydroxyphenylcinnoline, was an oil. The properties of the latter suggested instability—for example, the oil was soluble in acetone giving a brilliant blue solution, the colour of which faded completely after some hours' exposure to the air; this behaviour, also, is reminiscent of that shown by alkylphenazonium salts, which give rise to free radicals (McIlwain, *loc. cit.*). Qualitative similarity between the reactions of the two series of salts was further suggested by the observation that, under suitable conditions, the decomposition of the cinnolinium salt is accompanied by nuclear iodination with formation of *x*-iodo-4-*p*-hydroxyphenylcinnoline; this is almost certainly a case of anionoid substitution, which is a characteristic feature of the decomposition of phenazonium salts (McIlwain, *loc. cit.*).

The resemblance between the decompositions of cinnolinium and of phenazonium salts is not unexpected in view of the vinylogous relationship existing between the location of the nitrogen atoms in the two heterocyclic systems. The reaction may not, however, be characteristic of all 4-arylcinnolinium compounds; for example, 4-phenyl-3-methylcinnoline ethiodide did not show this behaviour, and the following observations clearly indicate that the nature of the 4-substituent profoundly influences the reaction.

From 6-chloro-4-aminocinnoline (Part XVII, in the press) was obtained an excellent yield of the methiodide (IV), which on treatment with a large excess of alkali hydroxide at room

temperature was converted into the methohydroxide (or pseudo-base). This substance was stable at room temperature, but in hot alkaline solution decomposed into ammonia and 6-chloro-1-



methyl-4-cinnolone (V). The structure of (V) (the major product of the reaction) follows from its identity with the product of the action of methyl sulphate on 6-chloro-4-hydroxycinnoline, whereas treatment of 4:6-dichlorocinnoline with sodium methoxide furnished the isomeric 6-chloro-4-methoxycinnoline (VI). The position of quaternary salt formation in 6-chloro-4-aminocinnoline is thus established as N_1 ; this is, therefore, the basic centre of this substance, and probably of other Bz-substituted 4-aminocinnolines (Part XVII) also.

This evidence, taken in conjunction with the properties of 4-methylcinnolines described in Part XII (*J.*, 1947, 808), lends strong support to the suggestion (*loc. cit.*) that the basic nitrogen of all 4-substituted cinnolines is N_1 ; the alternative thesis, namely that the centre of basicity could be shifted from N_1 to N_2 by the introduction of suitable 4-substituents, now becomes a more remote contingency. It should be noted, however, that formal proof of this point is still lacking for 4-hydroxycinnolines; the fact that in these substances alkylation occurs at N_1 is irrelevant, because *N*-alkylation of any hydroxylated nitrogenous heterocyclic ring involves triad or pentad prototropy, irrespective of basicity. It happens that in 4-hydroxycinnolines N_1 functions in both capacities, but this need not always be so, and our experience with certain quinazoline derivatives (Morley and Simpson, in the press) has in fact demonstrated that in these compounds the positions of quaternary salt formation and *N*-alkylation are probably not identical.

The decomposition of (IV) also gave rise to small amounts of two other substances of unknown structure. One of these was a neutral compound (substance X), isomeric with (V) and (VI), which could not be hydrolysed under mild conditions; the formation of this compound was apparently independent of the pH of the medium provided alkalinity was maintained. The other compound was an iodide, m. p. 238°, isolated from faintly acid solution.

EXPERIMENTAL.

(Melting points are uncorrected.)

4-Phenyl-3-methylcinnoline Ethiodide.—A solution of the cinnoline (3 g.) in alcohol (15 c.c.) and ethyl iodide (7.5 c.c.) was refluxed for 4 hours. Concentration and cautious addition of ether precipitated the crude ethiodide, which separated from alcohol in soft, light-red needles, m. p. 206–207° [Found: C, 53.85; H, 4.8; I (mean of several inconsistent values), 35.3. $C_{17}H_{11}N_2I$ requires C, 54.25; H, 4.55; I, 33.75%]. On the small scale, decomposition of the salt with aqueous sodium hydroxide at room temperature gave an amorphous basic solid from which no 4-phenyl-3-methylcinnoline could be isolated, and which did not give a crystalline picrate.

3-Phenyl-4-p-hydroxyphenylcinnoline Ethiodides.—A suspension of the cinnoline (2.5 g.) in alcohol (30 c.c.) and ethyl iodide (10 c.c.) was refluxed for 7 hours, a clear dark-coloured solution being gradually formed. On concentration, a mixture (2.35 g.) separated, from which substantially pure monoethiodide (0.9 g.) was obtained by recrystallisation from alcohol; the pure compound formed clusters of small orange leaflets, m. p. 227–228° (decomp.) (Found: C, 58.15; H, 4.45; I, 26.35. $C_{22}H_{19}ON_2I$ requires C, 58.15; H, 4.2; I, 28.0%). It (400 mg.) was decomposed by hot *N*-sodium hydroxide (10 c.c.) (an intensely purple-crimson solution was produced) with regeneration of the original cinnoline (130 mg., m. p. 283–285°, mixed m. p. 284–286°); no search for other products was made, but the odour of acetaldehyde was observed during the decomposition [cf. the decomposition of 4-*p*-hydroxyphenylcinnoline ethiodide (*q.v.*)]. The salt gave an intense crimson solution in concentrated sulphuric acid; on dilution the colour faded and a precipitate was formed.

The filtrate from the crude monoethiodide (from another experiment) was concentrated further; the resultant solid, after several crystallisations from alcohol, formed deep ruby-red blades, m. p. 216–217°

(190—195° when mixed with the monoethiodide), and from analysis appeared to consist principally of a diethiodide (Found: C, 44.7; H, 3.25; I, 37.5. $C_{14}H_{11}ON_2I_2$ requires C, 47.2; H, 4.0; I, 41.6%).

Addition of a drop of piperidine to an alcoholic solution of the mixed ethiodides gave an intense green colour, becoming deep blue-green on dilution. Addition of acid to this solution destroyed the colour, which was restored (purple) by ammonia or sodium carbonate with precipitation at an intermediate stage of an amphoteric solid.

Preparation and Alkaline Decomposition of 4-p-Hydroxyphenylcinnoline Ethiodide.—The cinnoline (10 g.), alcohol (200 c.c.), and ethyl iodide (80 c.c.) were refluxed for 4 hours. The ethiodide, obtained by concentration, crystallised from alcohol in scarlet prisms, m. p. 237—239° (Found: C, 51.15; H, 4.15. $C_{14}H_{11}ON_2I$ requires C, 50.8; H, 4.0%; satisfactory iodine figures could not be obtained); yield of nearly pure compound, 13 g. The salt gave a deep crimson solution in concentrated sulphuric acid, becoming yellow on dilution. Addition of piperidine to an alcoholic solution produced a very intense purple colour, discharged by acid and restored by ammonia or sodium carbonate solution.

The following alkaline decompositions of the salt were carried out.

(a) A solution of the salt (1 g.) in warm water (80 c.c.) was treated with 2N-sodium carbonate (20 c.c.) and heated at 90—95°; nitrogen was bubbled through the liquid, and the issuing gases were passed into a solution of 2:4-dinitrophenylhydrazine (0.6 g.) in 10% sulphuric acid (66 c.c., v/v). After 1 hour the precipitated hydrazone was collected (0.43 g., m. p. 143—144°) and recrystallised from alcohol, yielding flat yellow needles, m. p. 166.5—167.5° alone and mixed with authentic acetaldehyde 2:4-dinitrophenylhydrazone. The alkaline solution in the reaction flask was acidified with acetic acid, giving almost pure 4-p-hydroxyphenylcinnoline (0.45 g.), m. p. 229—231°, and 232—233° (alone and in admixture with authentic material) after crystallisation from alcohol.

(b) An experiment carried out as in (a) except that the sodium carbonate was replaced by 2N-sodium hydroxide (20 c.c.) gave 4-p-hydroxyphenylcinnoline in identical yield and purity, but only 0.15 g. of crude aldehyde dinitrophenylhydrazone (m. p. 129—135°). From this, a small amount of acetaldehyde 2:4-dinitrophenylhydrazone, m. p. 161—163°, was obtained by repeated crystallisation from alcohol. Apparently other aldehydes had been present (probably formed by self-condensation of the acetaldehyde), but these were not identified. The identity of the cinnoline obtained in this and the preceding experiment was confirmed by acetylating the combined crops; 4-p-acetoxyphenylcinnoline (preceding paper), m. p. and mixed m. p. 127.5—128.5°, was thus obtained.

(c) A solution of the salt (2 g.) in water (240 c.c.) and 2N-sodium carbonate (40 c.c.) was left for 4 months in an uncorked flask at laboratory temperature. The solid which had separated was collected and washed with water until the washings were colourless; 0.95 g., m. p. 237—241°. As it could not be purified by crystallisation, the whole was acetylated (boiling acetic anhydride) and freed from solvent in an evacuated desiccator. The residue was repeatedly crystallised from benzene-ligroin (b. p. 60—80°), yielding α -iodo-4-p-acetoxyphenylcinnoline as stout, pale yellow polyhedra, m. p. 158—160° (Found: C, 50.2; H, 2.9; N, 7.9; I, 33.55. $C_{14}H_{11}O_2N_2I$ requires C, 49.2; H, 2.85; N, 7.2; I, 32.6%). From a small-scale experiment in which the alkaline solution had stood for only 10 weeks a mixture was isolated which could not be purified by direct crystallisation but which (m. p. 243—244°) contained iodocinnoline (Found: I, 18.35. Calc. for $C_{14}H_9ON_2I$: I, 36.5%); pure 4-p-acetoxyphenylcinnoline was readily isolated by acetylation of the more soluble material.

(d) In other experiments in which sodium and ammonium hydroxide were used, the reaction mixtures were extracted with ether before acidification; small amounts of a brown oil were thus obtained, which was easily soluble in acetone giving a brilliant and very intense purple solution, the colour of which faded perceptibly during 2 hours' exposure to the air, and completely on standing overnight.

(e) A solution of the salt (0.5 g.) in water (45 c.c.) and 4N-ammonia (5 c.c.) was left at laboratory temperature for 10 weeks in an open flask. A sticky solid separated during this time, from which unchanged quaternary salt was isolated (by extraction with hot water) as the only identifiable product.

6-Chloro-4-methoxycinnoline.—A solution of 4:6-dichlorocinnoline (2 g.; this vol., p. 917) and sodium methoxide (0.8 g.) in methyl alcohol (50 c.c.) was refluxed for 20 minutes, cooled, acidified with acetic acid, and diluted with water. The precipitate was filtered off, washed, and recrystallised from methyl alcohol, from which 6-chloro-4-methoxycinnoline (1.5 g.) separated in colourless narrow blades, m. p. 169.5—170° (Found: C, 55.6; H, 3.9; N, 13.9. $C_9H_7ON_2Cl$ requires C, 55.5; H, 3.6; N, 14.4%).

6-Chloro-1-methyl-4-cinnolone.—Methyl sulphate (2 c.c.) was added to a slightly warm solution of 6-chloro-4-hydroxycinnoline (2 g.; *J.*, 1945, 520) in aqueous potassium hydroxide (20%, 40 c.c.). The mixture was heated on the steam-bath, separation of the product (2 g., m. p. 188—200°) occurring almost immediately. After several crystallisations from water containing a little 2N-hydrochloric acid, and finally from alcohol, 6-chloro-1-methyl-4-cinnolone separated in stout, pale yellow, brittle needles, m. p. 221—222° after previous shrinking (Found: C, 55.85; H, 4.0; N, 14.2. $C_9H_7ON_2Cl$ requires C, 55.5; H, 3.6; N, 14.4%). Although the free base separates from dilute hydrochloric acid, it is distinctly more soluble therein than in water alone (from which it forms long, silky needles).

Preparation and Alkaline Decomposition of 6-Chloro-4-aminocinnoline Methiodide.—Prepared from 6-chloro-4-aminocinnoline (Part XVII, in the press) (8 g.), alcohol (100 c.c.), and methyl iodide (20 c.c.) (3½ hours under reflux), 6-chloro-4-aminocinnoline methiodide (crude yield, 12.1 g.) crystallised from hot water in long, saffron-coloured needles, m. p. 225—226° (decomp.) (Found: C, 32.35; H, 3.2; N, 12.5. $C_9H_7N_3ClI \cdot 0.5H_2O$ requires C, 32.7; H, 3.05; N, 12.7%. Halogen determinations were unsatisfactory). The following procedure was the outcome of several preliminary experiments.

A solution of the salt (4 g.) in water (160 c.c.) was treated with 2N-sodium hydroxide (100 c.c.) and left at laboratory temperature. The dark oil which soon separated from the green solution changed overnight to a mass of soft, almost colourless needles, which (1.5 g.) were filtered off (filtrate A) and, without purification (the substance was unstable and could not be recrystallised), dissolved in 50% aqueous acetic acid (10 c.c.) (solution B). One half of this solution was brought to pH 9 with sodium hydroxide and boiled gently for ½ hour; a little ammonia was evolved. The solution was diluted

somewhat with water and filtered hot (charcoal); a solid separated on cooling, which on recrystallisation from water yielded substance X in long, colourless needles, m. p. 162–163°, which gave a positive Beilstein halogen test (Found: C, 55.9; H, 3.7; N, 14.4, 14.7. $C_9H_7ON_2Cl$ requires C, 55.5; H, 3.6; N, 14.4%). This substance was less soluble in water than 6-chloro-1-methyl-4-cinnolone, and crystallised well from benzene. It gave a marked depression in melting point when mixed with 6-chloro-4-methoxycinnoline. It showed no basic or acidic properties, and was unaffected by short boiling with dilute hydrochloric acid or sodium hydroxide. The first filtrate from substance X was made alkaline to thymolphthalein (sodium hydroxide) and boiled; ammonia was again evolved, and recrystallisation (water; charcoal) of the solid which separated from the hot solution yielded 6-chloro-1-methyl-4-cinnolone, m. p. and mixed m. p. 220–221°. The other half of solution B was made strongly alkaline with sodium hydroxide and boiled; substance X and 6-chloro-1-methyl-4-cinnolone were separated (by the use of dilute hydrochloric acid) and identified (m. p. and mixed m. p.).

Filtrate A was divided into 2 parts. One was decomposed at pH 11 by boiling, and yielded ammonia, 6-chloro-1-methyl-4-cinnolone, and substance X. The other part was brought to pH 6 with acetic acid, boiled for 20 minutes, and concentrated on the steam-bath to 2/3 volume. The mixture which separated gave 6-chloro-1-methyl-4-cinnolone as the least soluble component, and the early filtrates from this compound contained an iodide; this salt, after several crystallisations from alcohol, formed yellow rosettes of small needles, m. p. 237–238° (Found: C, 43.05; H, 3.95; N, 12.6%).

Similar results to the above were obtained when the original treatment of the quaternary salt with sodium hydroxide was performed under nitrogen.

The author is indebted to Imperial Chemical Industries Limited (Dyestuffs Division) for various facilities, and to the Council of the Durham Colleges for a grant from the Research Fund during the early part of this investigation.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
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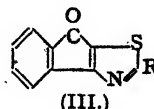
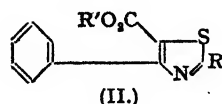
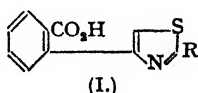
[Received, February 18th, 1947.]

330. Miscellaneous Thiazoles.

EDWARD B. KNOTT.

Derivatives of 4-o-carboxyphenylthiazole (I) and 4-phenylthiazole-5-carboxylic acid (II) prepared by standard methods could not be cyclised to indonothiazoles (III). Phenylthiobiuret and α -halogeno-ketones react together to give *azamethin* bases (IV). A few new thiazyl sulphides have been prepared. 2-Chloroacetyl furan and 2-bromoacetyl furan have been obtained crystalline and converted into derivatives of 4-(2'-furyl)thiazole (VI). 2-Chloroacetylpyrrole condenses normally with thiourea and normally with thioacetamide in the presence of alkali to give derivatives of 4-(2-pyrrolyl)thiazole (VII), but abnormally with alkyl dithiocarbamates to give di-(2-pyrrolylmethyl) sulphide (VIII).

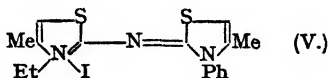
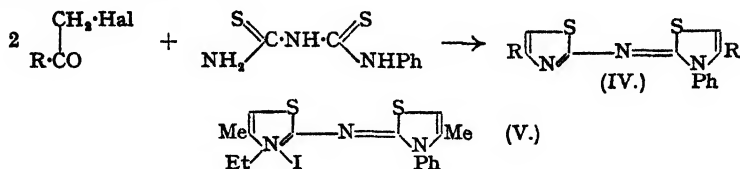
THE formation of polycarbocyclic thiazoles by intramolecular ring closure of 4-arylthiazole-5-acetic acids has been reported recently (Knott, J., 1945, 455). In attempts to prepare indonothiazoles (III) by analogous methods two types of intermediate were required, namely, a 4-o-carboxyphenylthiazole (I) and a 4-phenylthiazole-5-carboxylic acid (II; $R' = H$). (I) was readily prepared from o-carboxyphenacyl bromide and (II; $R' = Et$) from ethyl α -bromobenzoylacetate or the chloro-analogue (Hirst, Macbeth, and Traill, *Proc. Roy. Irish Acad.*, 1925, 37B, 47). Hydrolysis of (II; $R = Me$, $R' = Et$) gave the required acid, but where $R = NH_2$ simultaneous loss of carbon dioxide gave 2-amino-4-phenylthiazole. Ethyl α -bromobenzoylacetate condensed with ethyl and isopropylthioncarbamates to give ethyl 2-hydroxy-4-phenylthiazole-5-carboxylate (II; $R = OH$, $R' = Et$); the simultaneous loss of the alkyl group was also observed by Hantzsch and Hubacher (*Annalen*, 1890, 259, 250) whilst employing chloroacetone.



All cyclisation experiments on the acids or esters were unsuccessful.

The condensation of dithiomalonamides with α -halogeno-ketones has been described by Lehr, Guex, and Erlenmeyer (*Helv. Chim. Acta*, 1944, 27, 972) who thus obtained dithiazolylmethanes. Some time ago an analogous reaction was applied to phenylthiobiuret which condensed very readily with chloroacetone and phenacyl bromide to give *azamethin* bases (IV). Where $R = Me$ (IV) formed an *ethiodide* which is [2-(4-methyl-3-ethylthiazole)][2-(3-phenyl-

4-methylthiazole]azamethincyanine iodide (V). This pale yellow dye does not sensitise a photographic silver chloride emulsion.

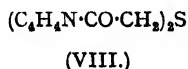
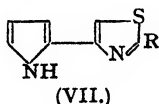
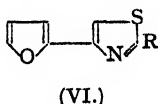


Using the method of Buchman, Reims, and Sargent (*J. Org. Chem.*, 1941, 6, 764) for the direct formation of 2-alkylthiothiazoles by the condensation of chloroacetone and methyl dithiocarbamate, 2-alkylthio-4-phenylthiazoles and 2-benzylthio-4-phenylthiazole have been prepared.

As intermediates for photographic sensitising dyes, 4-(2'-furyl)-* and 4-(2'-pyrryl)-thiazoles containing a reactive substituent in the 2-position were required.

2-Chloroacetylfuran, one of the intermediates for the preparation of the above thiazoles, has been obtained as an oil by Gilman and Burtner (*J. Amer. Chem. Soc.*, 1935, 57, 911), and by Burger and Harnest (*ibid.*, 1943, 65, 2382); it has now been found to crystallise readily at room temperature as did also 2-bromoacetylfuran. 2-Chloroacetylpyrrole, the second required intermediate, was obtained in 20% yield from pyrrole and chloromethyl cyanide by Blicke, Faust, Gearien, and Warzynski (*J. Amer. Chem. Soc.*, 1943, 65, 2465). Using this method with slight variations, a 35% yield was obtained.

The halogeno-acetylfuran condensed normally with thiourea, thioacetamide, and methyl dithiocarbamate to give the 2-amino-, 2-methyl-, and 2-methylthio-derivatives of 4-(2'-furyl)-thiazole (VI; R = NH₂, Me, SMe).



2-Chloroacetylpyrrole condensed normally with thiourea giving the hydrochloride of 2-amino-4-(2'-pyreryl)thiazole (VII; R = NH₂) as sole product. With thioacetamide, however, condensation in alcohol gave a deep red solution, and the resultant product was difficult to purify. The formation of dye was prevented, however, in the presence of alkali carbonate and the main reaction product was the expected 4-(2'-pyreryl)-2-methylthiazole (VII; R = Me) although an appreciable amount of a crystalline solid was obtained, which was not volatile in steam. With methyl dithiocarbamate the chloro-ketone gave chiefly a purple dye in the absence of alkali. The addition of alkali carbonate again prevented dye formation, but the product obtained was identical with the by-product obtained in the thioacetamide condensation. It is di-(2-pyrroyl-methyl) sulphide (VIII). The same product was obtained from the chloro-ketone and ethyl dithiocarbamate, ammonium dithiocarbamate, or sodium sulphide. The mechanism of this abnormal reaction is probably analogous to the formation of substituted diquinolyl sulphides from chloroquinolines and thiourea (Rosenhauer, Hoffmann, and Heuser, *Ber.*, 1929, 62, 2730; Renfrew, *J. Amer. Chem. Soc.*, 1946, 68, 1433) and of other diheterocyclyl sulphides from heterocyclyl chlorides and thiourea (Surrey and Lindwall, *J. Amer. Chem. Soc.*, 1940, 62, 1697; Watt, *J. Org. Chem.*, 1939, 4, 436).

EXPERIMENTAL

(Analyses are by Drs. Weiler and Strauss, Oxford: m. ps. are not corrected.)

4-o-Carboxyphenyl-2-methylthiazole (I; R = Me). *o*-Carboxyphenacyl bromide (1.22 g.; 0.005 mol.) (Gabriel and Michael, *Ber.*, 1877, 10, 1551) and thioacetamide (0.375 g.; 0.005 mol.) gave the hydrobromide on refluxing together for 15 minutes in isopropyl alcohol (2.5 c.c.). The base, m. p. 143–147°, formed colourless needles from aqueous methyl alcohol (Found: S, 14.5. $C_{11}H_9O_2NS$ requires S, 14.65%). **2-Amino-4-o-carboxyphenylthiazole** (I; R = NH_2), obtained similarly from thiourea (0.38 g.), formed soft needles, m. p. 174° (decomp.), from alcohol. The needles contained solvent of crystallisation removed by drying at 115°/20 mm. (Found: S, 14.7. $C_{11}H_9O_2NS$ requires S, 14.56%).

4-Phenyl-2-methylthiazole-5-carboxylic Acid (II; R = Me, R' = H). Thioacetamide (0.75 g.; 0.01 mol.), ethyl α -bromobenzoylacetate (2.6 g.; 0.01 mol.), and isopropyl alcohol (10 c.c.) were refluxed

* Since this paper was written, B.P. 571,077 has appeared describing the condensation of 2-bromoacetyl-furan (obtained by bromination of 2-acetyl-furan) with thioacetamide to give 4-(2'-furyl)-2-methyl-thiazole.

for 15 minutes, diluted with aqueous sodium carbonate, and the precipitated oil taken up in ether which was dried, the ether then being removed. The oil could not be crystallised. It was dissolved in alcohol (5 c.c.) and shaken with 10% aqueous hydroxide (2 c.c.), then allowed to stand for 3 hours. The acid obtained on acidification formed pink tablets, m. p. 216° (decomp.), from alcohol (Found: S, 14.45. $C_{11}H_9O_2NS$ requires S, 14.65%).

Ethyl 2-Amino-4-phenylthiazole-5-carboxylate.—This, obtained similarly from ethyl α -bromobenzoylacetate and thiourea, formed thick, pale yellow needles, m. p. 173° (Hirst *et al.*, *loc. cit.*, give m. p. 173°) from methyl alcohol (Found: S, 12.85. Calc. for $C_{12}H_{13}O_2N_2S$: S, 12.9%). The ester (1.0 g.) was dissolved in hot alcohol (20 c.c.), 10% aqueous sodium hydroxide (2 c.c.) was added, and after 30 minutes at 50° the solution was neutralised with dilute acetic acid, giving colourless needles of 2-amino-4-phenylthiazole, m. p. 151°, not depressed on admixture with authentic specimen obtained from phenacyl bromide and thiourea (Found: S, 17.95. Calc. for $C_8H_7N_2S$: S, 18.2%).

Ethyl 2-Hydroxy-4-phenylthiazole-5-carboxylate (II; R = OH, R' = Et).—Ethyl α -bromobenzoylacetate (2.6 g.; 0.01 mol.), ethyl thioncarbamate (1.05 g.; 0.01 mol.) or isopropyl thioncarbamate (1.19 g.), and isopropyl alcohol (5 c.c.) were boiled together for a few minutes. The liquor clouded and deposited pale yellow needles, which then formed colourless needles from alcohol, m. p. 202°, soluble in ammonia (Found: S, 12.9. $C_{13}H_{11}O_3NS$ requires S, 12.85%).

Azamethin[2-(4-phenylthiazole)][2-(3:4-diphenyl-2:3-dihydrothiazole)] (IV; R = Ph).—Phenacyl bromide (0.4 g.; 0.002 mol.) was added to a hot solution of phenyldithiobiuret (0.215 g.; 0.01 mol.) in absolute ethyl alcohol (10 c.c.) and refluxed for 15 minutes. To this solution was then added anhydrous sodium carbonate (1.1 g.) and the mixture refluxed for a further 15 minutes. Addition of water (100 c.c.) precipitated the base as a solid which formed colourless needles (0.4 g.), m. p. 228—230°, from benzene-light petroleum (Found: C, 70.7; H, 4.1; N, 9.85. $C_{24}H_{17}N_4S_2$ requires C, 70.0; H, 4.15; N, 10.2%). The dihydrobromide was obtained if the carbonate addition was omitted and the mixture concentrated after 1 hour. From isopropyl alcohol it formed yellow prisms, m. p. 152° (Found: HBr, 28.25. $C_{24}H_{17}N_4S_2 \cdot 2HBr$ requires HBr, 28.25%).

Azamethin[2-(4-methylthiazole)][2-(3-phenyl-4-methyl-2:3-dihydrothiazole)] (IV; R = Me).—By proceeding as above but using phenyldithiobiuret (1.07 g.) and chloroacetone (0.92 g.), the base was obtained as faintly yellow needles, m. p. 170—171°, from alcohol (Found: S, 22.25. $C_{14}H_{13}N_2S_2$ requires S, 22.35%).

[2-(4-Methyl-3-ethylthiazole)][2-(3-phenyl-4-methylthiazole)]azamethincyanine Iodide (V).—The base (IV; R = Me) (1 g.) and ethyl iodide (1 c.c.) were heated for 8 hours in a sealed tube on the steam-bath. From methanol the ethiodide formed yellow needles, m. p. 190—192° (Found: S, 14.7. $C_{15}H_{16}N_2IS_2$ requires S, 14.45%).

2-Alkylthio- and 2-Benzylthio-4-phenylthiazoles.—Molar quantities of phenacyl bromide and the dithiocarbamic ester were refluxed for 15 minutes in ethyl alcohol. The hydrobromides were obtained on concentration. 2-Methylthio-4-phenylthiazole was obtained in colourless needles, m. p. 24°, from benzene (Levi, *Gazzetta*, 1931, 61, 719, describes it as an oil) (Found: S, 30.8. Calc. for $C_{10}H_9NS_2$: S, 30.95%). The hydrobromide formed colourless prisms, m. p. 194—196°, from isopropyl alcohol. The crystals contain the solvent, removed at 115° (Found: S, 22.3. $C_{10}H_9NBrS_2$ requires S, 22.25%). 2-Ethylthio-4-phenylthiazole was obtained as a viscous oil, b. p. 300° (partial decomp.) (Found: S, 29.9. $C_{11}H_{11}NS_2$ requires S, 28.3%). The hydrobromide formed colourless needles, m. p. 167—169°, from isopropyl alcohol. The crystals contain solvent removed at 115° (Found: S, 21.35. $C_{11}H_{11}NBrS_2$ requires S, 21.25%). 2-Benzylthio-4-phenylthiazole formed glassy crystals, m. p. 56—57°, from benzene-light petroleum (Found: S, 22.5. $C_{14}H_{13}NS_2$ requires S, 22.65%). Its hydrobromide had m. p. 192°.

2-Halogenoacetylfurans.—The method employed was essentially that of Burger *et al.* (*loc. cit.*). The furoyl chloride was treated with ethereal diazomethane until the powerful lachrymatory action of the chloride could not be detected on removing a spot of the reaction mixture. Dry hydrogen chloride or bromide was used to decompose the diazo-compound. 2-Chloroacetyl furan, b. p. 125°, solidified after distilling twice. From benzene-light petroleum it formed colourless leaflets, m. p. 30.5°, in 86% yield (Found: Cl, 24.25. Calc. for $C_6H_5O_2Cl$: Cl, 24.55%) (Burger *et al.* report b. p. 93—108°; Gilman *et al.* b. p. 127—129°). 2-Bromoacetyl furan, b. p. 126°, formed colourless leaflets, m. p. 34°, from benzene-light petroleum in 87% yield (Found: Br, 42.15. $C_6H_5O_2Br$ requires Br, 42.4%).

2-Amino-4-(2-furyl)thiazole.—Thiourea (0.38 g.; 0.005 mol.) and chloroacetyl furan (0.722 g.; 0.005 mol.) were dissolved in hot ethyl alcohol (5 c.c.), anhydrous sodium carbonate (0.026 g.; 0.025 mol.) was added, and the mixture refluxed for 5 minutes. On addition of water the thiazole separated. From benzene-light petroleum it formed glistening flat needles, m. p. 124.5°, in 95% yield (Found: S, 19.45. $C_7H_7ON_2S$ requires S, 19.3%).

4-(2'-Furyl)-2-methylthiazole.—Thioacetamide (7.5 g.; 0.1 mol.) and 2-bromoacetyl furan (18.9 g.; 0.1 mol.) were covered with ethyl alcohol (20 c.c.) and warmed gently. Heat was suddenly evolved and after cooling, the required hydrobromide separated, the precipitation being completed by addition of ether. It formed pale brown needles, m. p. 194—196°, from methanol-ether in 87% yield (Found: Br, 32.6; S, 12.85. C_8H_9ONBrS requires Br, 32.5; S, 13.05%). The base was obtained as an oil, b. p. 128°, possessing a strong thiazole odour* (Found: S, 19.35. C_8H_9ONS requires S, 19.4%).

2-Methylthio-4-(2'-furyl)thiazole.—Obtained as for the 2-methyl analogue, the hydrobromide (70% yield) formed tiny plates, m. p. 208—210° (decomp.), from ethyl alcohol-ether (Found: Br, 28.9. $C_8H_9ONBrS_2$ requires S, 28.95%). The base was obtained as a heavy oil, b. p. 177°, with an odour like that of mushrooms (Found: S, 32.4. $C_8H_9ONS_2$ requires S, 32.55%).

2-Chloroacetylpyrrole.—The procedure according to Blicke *et al.* (*loc. cit.*) was followed, but the reaction mixture of the ketimine hydrochloride was allowed to stand for 18 hours before filtration, the hydrolysis solution made neutral to Congo-red with sodium acetate before being heated, and the required product extracted from the resin by repeated refluxing with carbon tetrachloride. With these variations, a 36% yield was obtained.

* B.P. 571,077 gives b. p. 120—130° but no analysis.

2-Amino-4-(2'-pyrryl)thiazole.—Obtained like the furyl analogue, the *base* formed creamy needles, m. p. 160°, from hot water (Found: N, 24.9; S, 19.4. $C_8H_7N_2S$ requires N, 24.45; S, 19.4%). The hydrochloride, m. p. 200° (decomp.), formed greenish needles from alcohol.

4-(2'-Pyrryl)-2-methylthiazole.—Thioacetamide (1.5 g.; 0.02 mol.) and 2-chloroacetylpyrrole (2.87 g.; 0.02 mol.) were dissolved in warm ethyl alcohol (10 c.c.) and excess of anhydrous sodium carbonate (1.0 g.) was added. The whole was refluxed for 30 minutes, the flask being shaken well every time a red coloration developed. On dilution with water an oil was precipitated which solidified. The solid (3.2 g.) was subjected to steam distillation giving 2.5 g. of the steam-volatile thiazole, obtained as glassy aggregates, m. p. 94–95°, from methanol (Found: S, 19.85. $C_8H_8N_2S$ requires S, 19.55%). It can also be purified by distillation (b. p. 171°) or by recrystallisation of the crude condensate from methanol. The residue from the steam distillation (0.5 g.) formed colourless needles, m. p. 179°, from acetone.

Di-(2-pyrrolylmethyl) Sulphide.—(a) 2-Chloroacetylpyrrole (1.435 g.; 0.01 mol), and methylthiocarbamate (1.07 g.; 0.01 mol.) or ethyl dithiocarbamate (1.21 g.), were dissolved in warm ethyl alcohol (5 c.c.) and, after the addition of anhydrous sodium carbonate (1.0 g.) to avoid dye formation, the whole was refluxed for 30 minutes. The precipitate obtained on dilution with water gave needles on recrystallisation from alcohol, m. p. 179–180°, which fluoresced yellow in ultra-violet light. They were identical with the by-product from the thioacetamide condensation.

(b) Equimolecular amounts of 2-chloroacetylpyrrole and ammonium dithiocarbamate were refluxed in alcohol for 10 minutes. Ammonium chloride was precipitated. On dilution with water the sulphide was precipitated, m. p. 179°, mixed m. p. with (a) 179°.

(c) 2-Chloroacetylpyrrole (2 mol.) and sodium sulphide (1 mol.) gave the sulphide after being refluxed for 10 minutes in alcohol. The *product* had m. p. 179° and did not depress the m. p. of the specimens obtained under (a) and (b) (Found: C, 58.25; H, 4.8; N, 11.2; S, 12.95. $C_{12}H_{12}O_2N_2S$ requires C, 58.05; H, 4.85; N, 11.3; S, 12.95%).

RESEARCH LABORATORIES, KODAK LIMITED,
WEALDSTONE, HARROW, MIDDLESEX.

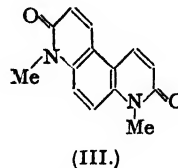
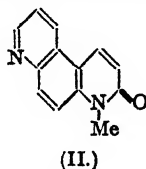
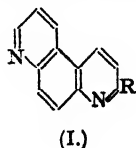
[Received, January 17th, 1947.]

331. *Attempts to find New Antimalarials. Part XXVI. Further Derivatives of p-Phenanthroline.*

By BRYCE DOUGLAS, REX G. JACOMB, and WILLIAM O. KERMACK.

2-Chloro-*p*-phenanthroline has been prepared by the action of phosphorus oxychloride and pentachloride on (a) 1-methyl-*p*-phenanthrol-2-one (II) and (b) 2-hydroxy-*p*-phenanthroline (I; R = OH). The former was prepared either by the oxidation of *p*-phenanthroline methiodide with alkaline ferricyanide or from 6-amino-1-methylcarbostyryl by Skraup reaction; (I; R = OH) was similarly prepared from 6-aminocarbostyryl. Phosphorus oxychloride reacts with *p*-phenanthroline *N*-oxide to yield 2-chloro-*p*-phenanthroline (I; R = Cl), and with *p*-phenanthroline di-*N*-oxide to yield 2 : 7-dichloro-*p*-phenanthroline, which was independently synthesised by the action of phosphorus oxychloride and pentachloride on 2 : 7-diketo-1 : 8-dimethyl-1 : 2 : 7 : 8-tetrahydro-*p*-phenanthroline (III) obtained by oxidising the methiodide of 1-methyl-*p*-phenanthrol-2-one. Derivatives of *p*-phenanthroline with basic side chains have been prepared by condensation of 2-chloro-*p*-phenanthroline with appropriate amines.

CERTAIN derivatives of *p*-phenanthroline, including a number carrying basic side chains in positions 2 and 4, have been described by Kermack and Weatherhead (*J.*, 1940, 1164). 2-Chloro-*p*-phenanthroline (I; R = Cl) has now been prepared by oxidising the methiodide of *p*-phenanthroline with alkaline ferricyanide to 1-methyl-*p*-phenanthrol-2-one (II) followed by treatment of this with phosphorus oxychloride containing phosphorus pentachloride. That the chlorine atom in this compound is in fact in the 2-position was proved by preparing it from 6-aminocarbostyryl, which by means of a Skraup reaction was converted into 2-hydroxy-*p*-phenanthroline (I; R = OH), and the latter with phosphorus oxychloride and pentachloride readily yielded the same chloro-*p*-phenanthroline as that obtained by the other route. Further confirmation was obtained by an independent synthesis of 1-methyl-*p*-phenanthrol-2-one by means of a Skraup reaction on 6-amino-1-methylcarbostyryl.



An entirely different route for the synthesis of 2-chloro-*p*-phenanthroline has also been explored, similar to that used by Kermack and Tebrich (*J.*, 1945, 375) for the synthesis of 2-chloro-*m*-phenanthroline. When *p*-phenanthroline was treated with approximately 1 mol. of

perbenzoic acid the mono-*N*-oxide, m. p. 232—233°, along with some impure di-*N*-oxide was obtained. The di-*N*-oxide, m. p. 324—325°, was isolated from an experiment in which a larger proportion of perbenzoic acid was used, Evans and Linsker (*J. Amer. Chem. Soc.*, 1946, 68, 403) claim to have formed the di-*N*-oxide by the action of hydrogen peroxide on the base in acetic acid, but their m. p. (308°) is lower than ours. The action of phosphorus oxychloride on the mono-*N*-oxide gave 2-chloro-*p*-phenanthroline as main product; by treating the di-*N*-oxide in a similar way a compound, m. p. 315—316°, was isolated which was shown to be 2 : 7-dichloro-*p*-phenanthroline in the following way. The methiodide of 1-methyl-*p*-phenanthrol-2-one was oxidised with alkaline ferricyanide to 2 : 7-diketo-1 : 8-dimethyl-1 : 2 : 7 : 8-tetrahydro-*p*-phenanthroline which, when heated in a sealed tube at 150° for 24 hours with phosphorus oxychloride and pentachloride, yielded 2 : 7-dichloro-*p*-phenanthroline identical with a compound isolated from the product of the action of phosphorus oxychloride on the di-*N*-oxide of *p*-phenanthroline. An attempt was made to form the dimethiodide of *p*-phenanthroline by treating the base with methyl iodide under a variety of conditions including heating with a large excess of methyl iodide in nitrobenzene in a sealed tube, but the product consisted practically entirely of the monomethiodide.

As expected, 2-chloro-*p*-phenanthroline reacted readily with primary amines to form compounds such as 2-(2-diethylaminoethylamino)-, 2-(3-diethylaminopropylamino)-, and 2-(4-diethylamino-1-methylbutylamino)-*p*-phenanthroline, characterised respectively as trihydrobromide, trihydrobromide, and tris-3 : 5-dinitrobenzoate.

EXPERIMENTAL

p-Phenanthroline Methiodide.—*p*-Phenanthroline (25 g.) was heated under reflux with methyl iodide (100 c.c.) in nitrobenzene (250 c.c.) for 2 hours on a water-bath. Yellow needles of the methiodide separated during the reaction, and on cooling a further amount was deposited; the combined products were dried in a vacuum and recrystallised from water; yield 38 g., m. p. 270—271° (Found: I, 38.7. $C_{13}H_{11}N_2I$ requires I, 39.4%).

1-Methyl-*p*-phenanthrol-2-one.—(a) A mixture of 6-amino-1-methylcarbostyrl (3.9 g.), 69% sulphuric acid (42 g.), 80% arsenic acid (12 g.), and 90% glycerol (7.2 g.) was refluxed in an oil-bath for 2½ hours at 150°. The mixture, after dilution with an equal bulk of water followed by filtration, was made strongly alkaline with 10*N*-sodium hydroxide solution, and the precipitate collected. This brown solid was purified by prolonged extraction with ether (Sohxlet), the ether yielding 2.5 g., long yellow needles of 1-methyl-*p*-phenanthrol-2-one, m. p. 242° (Found: C, 74.2; H, 5.0. $C_{13}H_{10}ON_2$ requires C, 74.3; H, 4.8%).

(b) To a solution of potassium ferricyanide (21.9 g. in 200 c.c. of water) were added alternately small portions of solutions of *p*-phenanthroline methiodide (9 g. in 500 c.c. of water) and sodium hydroxide (4.2 g. in 100 c.c. of water). When the addition of both solutions had been completed, the mixture was set aside for ½ hour and then made strongly alkaline with 10*N*-sodium hydroxide (250 c.c.). The yellow precipitate was collected, dried on a porous plate, and extracted for 3—4 hours with benzene (250 c.c.) under reflux. After filtration, the process was repeated twice. On cooling, the benzene deposited 4.5 g. of a light yellow material, m. p. 245—246°, and on concentration a further 0.6 g. was obtained, m. p. 245—246°, mixed m. p. with 1-methyl-2-*p*-phenanthrolone, prepared as above, 243—244°.

2-Hydroxy-*p*-phenanthroline.—A mixture of 6-aminocarbostyrl (2.6 g.), arsenic acid (3.2 g.), concentrated sulphuric acid (4.4 g.), and glycerol (4.8 g.) was refluxed gently for 5 hours, then diluted with water to about 50 c.c. An inorganic brown solid (0.5 g.) was filtered off, and the filtrate, on neutralization with 10*N*-sodium hydroxide solution, deposited a brown solid which redissolved in excess of sodium hydroxide. The alkaline solution was neutralised with acetic acid and the precipitate which formed was filtered off, yielding 2.7 g. of a brown solid, m. p. 305—310°. Recrystallised several times from ethanol, 2-hydroxy-*p*-phenanthroline formed yellow needles, m. p. 302—303° (Found: C, 66.75; H, 5.0. $C_{12}H_8ON_2 \cdot H_2O$ requires C, 67.3; H, 4.7%).

2-Chloro-*p*-phenanthroline.—(1) From 2-hydroxy-*p*-phenanthroline. A mixture of 2-hydroxy-*p*-phenanthroline (1 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (10 c.c.) was refluxed for 32 hours in an oil-bath, almost complete solution then having taken place. The excess of oxychloride was removed by distillation in a vacuum, and the resulting mass treated with about 100 c.c. of water. Traces of a reddish oil separated and were removed by filtration. After the filtrate had been made slightly alkaline with 10*N*-sodium hydroxide solution, the white flocculent precipitate was filtered off and dried on the water-bath; yield 1.2 g. Recrystallised from aqueous ethanol, this yielded 0.7 g. of long white needles of 2-chloro-*p*-phenanthroline, m. p. 189—190° (Found: C, 66.6; H, 3.7. $C_{12}H_7N_2Cl$ requires C, 67.1; H, 3.3%).

(2) From 1-methyl-*p*-phenanthrol-2-one. A mixture of 1-methyl-*p*-phenanthrol-2-one (8 g.), phosphorus pentachloride (8 g.), and phosphorus oxychloride (48 c.c.) was divided into two parts and heated in two sealed tubes for 5 hours at 150°. After removal of excess of oxychloride by distillation in a vacuum, the reddish product was treated with ice, the solution made alkaline with ammonia, and the precipitate collected, washed with water, and dried on the water-bath, yielding 3.6 g. of a greyish-brown powder, m. p. 188°; recrystallised from ligroin, it formed white needles, m. p. 191° (Found: C, 67.1; H, 3.6%), showing no depression on admixture with a sample prepared as in (1).

p-Phenanthroline *N*-Oxide.—*p*-Phenanthroline (10 g., m. p. 172°), dissolved in dry chloroform (60 c.c.), was mixed with a solution of perbenzoic acid (8 g.) in chloroform (420 c.c.) (prepared as in *Org. Synth.*, Coll. Vol. I, 1st edn., p. 422). The mixture was kept below 0° for 24 hours, the chloroform removed, the

residue extracted four times with 10-c.c. portions of 2*N*-hydrochloric acid, and the extract rendered alkaline and extracted with chloroform (10-c.c. portions). The first six extracts on removal of the chloroform yielded material, m. p. 200—210° (4.5 g.), which after two recrystallisations from ethanol yielded white needles of *p*-phenanthroline *N*-oxide, m. p. 233—234° (3.5 g.) (Found: C, 73.8; H, 4.2. $C_{14}H_{11}N_2O$ requires C, 73.5; H, 4.1%). Further chloroform extracts yielded some impure di-*N*-oxide (2 g.).

p-Phenanthroline Di-*N*-oxide.—*p*-Phenanthroline (10 g., m. p. 172°), dissolved in dry chloroform (60 c.c.), was mixed with a solution of perbenzoic acid (12 g.) in chloroform (1030 c.c.) and kept below 0° for 2 days. Pale yellow needles, which separated, were collected, drained, washed with chloroform, and dried (11 g., m. p. 320—321°). The filtrate was evaporated to dryness, the residue extracted three times with 10-c.c. portions of 2*N*-hydrochloric acid, and the extract made alkaline with 10*N*-sodium hydroxide solution and extracted with chloroform. On removal of the chloroform, 0.2 g. of m. p. 309—310° was obtained. The total crude product was recrystallised from hot water, yielding white needles (8.8 g., m. p. 324—325°) (Found: C, 68.3; H, 4.1; N, 13.7. Calc. for $C_{14}H_{11}O_2N_2$: C, 67.9; H, 3.8; N, 13.2%).

2-Chloro-*p*-phenanthroline from *p*-Phenanthroline *N*-Oxide.—Phosphorus oxychloride (3 c.c.) was added to the dry oxide (1 g., m. p. 232—233°), heat being evolved. The mixture was refluxed for 2 hours at 120—125°, the excess of oxychloride removed in a vacuum, and the greyish syrup treated with cold water (25 c.c.). The solution was rendered alkaline with 10*N*-sodium hydroxide solution, the deposited solid collected after 24 hours, drained, washed with water, dried, and recrystallised from ethanol; yield 0.3 g., m. p. 190—191° undepressed on admixture with a specimen prepared as above.

2-Keto-1-methyl-1:2-dihydro-*p*-phenanthroline Methiodide.—1-Methyl-*p*-phenanthroline-2-one (0.6 g.) was heated under reflux with methyl iodide (4 c.c.) in nitrobenzene (10 c.c.) for 8 hours on a water-bath. The mixture was cooled, and the crystals collected, washed with fresh nitrobenzene, and dried, m. p. 289—290°. Recrystallisation from methanol gave yellow needles of 2-keto-1-methyl-1:2-dihydro-*p*-phenanthroline methiodide, m. p. 290—291° (Found: C, 47.9; H, 3.9. $C_{14}H_{13}N_2I$ requires C, 47.7; H, 3.7%).

2:7-Diketo-1:8-dimethyl-1:2:7:8-tetrahydro-*p*-phenanthroline.—A solution of sodium hydroxide (0.3 g.) in water (7.2 c.c.) and a solution of potassium ferricyanide (1.6 g.) in water (15 c.c.) were added alternately to a solution of 1-methyl-*p*-phenanthroline-2-one methiodide (0.7 g.) in water (36 c.c.), and the solution kept for $\frac{1}{2}$ hour at room temperature. The deposited crystals were collected and 10*N*-sodium hydroxide solution (18 c.c.) was added to the filtrate, whereupon more crystals separated; recrystallisation of the crude material from water gave yellow needles of 2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-*p*-phenanthroline (0.4 g., m. p. 363—364°) (Found: C, 67.0; H, 5.1; N, 11.3. $C_{14}H_{12}O_2N_2 \cdot \frac{1}{2}H_2O$ requires C, 67.5; H, 5.2; N, 11.2%).

2:7-Dichloro-*p*-phenanthroline.—(1) A mixture of the foregoing compound (0.2 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (3 c.c.) was heated in a sealed tube for 24 hours at 150°. The excess of oxychloride was decomposed with iced water, and the solution made strongly alkaline with 10*N*-sodium hydroxide solution. The deposited greyish material was collected, washed with water, dried in a vacuum, extracted with hot ethanol, and the concentrated extract allowed to crystallise, yielding white needles, m. p. 310—311°; further crystallisation from ethanol yielded 2:7-dichloro-*p*-phenanthroline, m. p. 315—316° (Found: C, 53.6; H, 2.7; N, 10.1. $C_{12}H_8N_2Cl_2 \cdot H_2O$ requires C, 53.9; H, 3.0; N, 10.5%).

(2) Phosphorus oxychloride (24 c.c.) was added to dry *p*-phenanthroline di-*N*-oxide (2 g.), heat being evolved. The mixture was heated at 125° for 5 hours, the excess of oxychloride removed in a vacuum, and the residue dissolved in 11*N*-hydrochloric acid (40—50 c.c.) to give a muddy brown solution which was rendered alkaline with 10*N*-sodium hydroxide solution to precipitate whitish material which was collected and dried, m. p. 240—250°. Prolonged extraction (1 day) with hot ethanol yielded 1 g. of material, m. p. 300—310°, which on recrystallisation from ethanol yielded 0.2 g. of 2:7-dichloro-*p*-phenanthroline, m. p. 315—316°; mixed m. p. with a sample prepared as above showed no depression.

2-(2-Diethylaminoethylamino)-*p*-phenanthroline.—2-Chloro-*p*-phenanthroline (0.4 g.) was refluxed with 2-diethylaminoethylamine (1 c.c.) at 140° for 3 hours. The excess of the latter was removed in a vacuum on a boiling water-bath to yield a solid yellow residue; this was dissolved in ethanol, and to it were added a few drops of ethanolic hydrobromic acid followed by a few drops of acetone, affording cream platelets of the hydrobromide (0.3 g.), m. p. 284—285° (Found: C, 40.0; H, 5.0. $C_{14}H_{22}N_4 \cdot 3HBr$ requires C, 40.2; H, 4.65%).

2-(3-Diethylaminopropylamino)-*p*-phenanthroline.—2-Chloro-*p*-phenanthroline (0.5 g.) was refluxed with 3-diethylaminopropylamine (1 c.c.) for 2 hours at 160°. When the product was worked up as above, but without addition of acetone, it afforded a hydrobromide which, recrystallised three times from ethanol, yielded pale yellow platelets (0.3 g.), m. p. 268—270° (Found: C, 39.9; H, 4.9; N, 9.8. $C_{14}H_{24}N_4 \cdot 3HBr \cdot H_2O$ requires C, 40.1; H, 5.1; N, 9.8%).

2-(4-Diethylamino-1-methylbutylamino)-*p*-phenanthroline.—2-Chloro-*p*-phenanthroline (0.2 g.) was refluxed with 4-diethylamino-1-methylbutylamine (0.4 c.c.) for 5 hours at 180°. The excess of reagent was removed in a vacuum, the syrupy residue dissolved in ethanol, and a few drops of a saturated ethanolic solution of 3:5-dinitrobenzoic acid added. An oil was deposited which solidified on standing for 2 weeks. The collected *tris*-3:5-dinitrobenzoate, recrystallised five times from ethanol, had m. p. 93—94° (Found: C, 51.8, 52.4; H, 4.8, 4.7; N, 14.1. $C_{21}H_{28}N_4 \cdot 3C_7H_4O_6N_2 \cdot C_2H_5OH$ requires C, 52.0; H, 4.5; N, 13.7%).

We have to acknowledge our indebtedness to Miss A. Weatherhead who first prepared *p*-phenanthroline *N*-oxide, and we thank the Medical Research Council for a grant which defrayed part of the expenses of this work.

332. The Crystal Structure of CsCuCl_3 and the Crystal Chemistry of Complex Halides ABX_3 .

By A. F. WELLS.

The crystal structure of CsCuCl_3 is determined. The crystals are hexagonal, $a = 7.20$, $c = 18.00$ Å.; space-group $C6_2$, with 6 molecules of CsCuCl_3 per cell. There are infinite chain ions of composition $(\text{CuCl}_3)_n^{2-}$ formed by planar CuCl_3 groups joined up by sharing two adjacent chlorine atoms, these ions being in the form of spirals around the six-fold screw axes. They are held together laterally by the caesium ions. The crystal chemistry of complex halides ABX_3 is discussed.

THE structure of the compound CsCuCl_3 is of interest both in connection with the stereochemistry of copper and also because of its close relation to a number of other halides ABX_3 , in which the A and X atoms together are close-packed. Except for the hydrated compounds $\text{CuCl}_3 \cdot 2\text{H}_2\text{O}$ (Harker, *Z. Krist.*, 1936, **93**, 136; MacGillavry and Bijvoet, *ibid.*, 1936, **94**, 231) and $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$ (Chrobak, *ibid.*, 1934, **88**, 35), little is known of the structures of cupric halides, simple or complex. The crystal structures of the cupric halides themselves are not known, and only the unit-cell dimensions and space-groups of the compounds KCuBr_3 (Silberstein, *Compt. rend.*, 1939, **209**, 540) and Cs_2CuCl_4 (Mellor, *Z. Krist.*, 1939, **101**, 160) have been determined. A note on CsCuCl_3 was published recently (Klug and Sears, *J. Amer. Chem. Soc.*, 1946, **68**, 1133) but the authors were unable to determine its crystal structure.

In the Periodic Table the elements around copper which exhibit bivalency are :

Mn	Fe	Co	Ni	Cu	Zn
			Pd	(Ag)	Cd

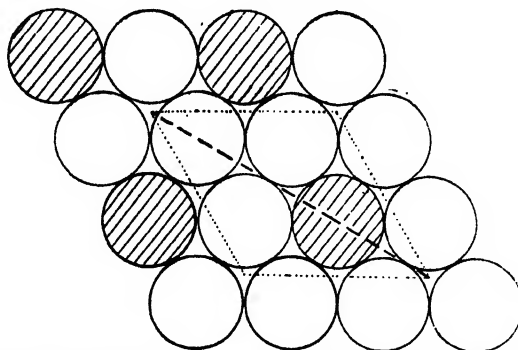
As regards its crystal chemistry Cu^{II} appear to be most closely related to Pd^{II} . For instance, the monoxides MnO , FeO , CoO , NiO , and CdO have the rock-salt structure, ZnO the wurtzite and the zinc-blende structure, but CuO a quite different structure, very similar to that of PdO , in which there is square co-ordination of the metal atoms by oxygen. The difluorides MnF_2 , FeF_2 , CoF_2 , NiF_2 , and ZnF_2 have the rutile structure, and CdF_2 the fluorite structure. CuF_2 apparently has neither of these structures (v. Wartenberg and Laves, *Z. anorg. Chem.*, 1939, **281**, 381); that of PdF_2 is unknown. The dichlorides of Mn, Fe, Co, Ni, Zn, and Cd all crystallise with the cadmium chloride structure, in which a metal atom forms six octahedral bonds, but crystalline PdCl_2 is built up of infinite chains in which each Pd forms four planar bonds. The bonds formed by the former elements in complex halides are discussed later. It will be shown in this paper that in CsCuCl_3 copper forms four planar bonds, again resembling Pd^{II} rather than the other elements mentioned above. The relation of the structure of CsCuCl_3 to that of CsAuCl_3 and other halides ABX_3 will be discussed later.

Determination of the Crystal Structure.—Crystals of CsCuCl_3 are readily grown from an aqueous solution containing caesium chloride and an excess of cupric chloride. The garnet-red crystals are hexagonal prisms $\{10\bar{1}0\}$ terminated by bipyramids, or, if grown slowly, essentially bipyramids $\{10\bar{1}1\}$. They are uniaxial and exhibit dichroism, the colour transmitted being brownish-red for vibrations along c and yellowish for vibrations perpendicular to c . No pyro-electric effect has been detected. The cell dimensions, $a = 7.20$ Å., $c = 18.00$ Å., are in good agreement with the values given by Klug and Sears (*loc. cit.*). The density, 3.65 g./c.c., indicates that the unit cell contains 6 CsCuCl_3 molecules. X-Ray photographs (Cu-K_α radiation) show that the Laue symmetry is $6/mmm$. The only systematic absences observed were in the orders $000l$, which appear only for $l = 6n$, indicating the space-group $C6_2$ (or $C6_2$). The crystal class 62 is consistent with the face development.

The cell dimensions are closely related to those of $\text{Cs}_3\text{Ti}_2\text{Cl}_9$ (Powell and Wells, *J.*, 1935, 1008; Hoard and Goldstein, *J. Chem. Physics*, 1935, **3**, 199), for which $a = 12.82$ ($=\sqrt{3} \times 7.40$), $c = 18.27$ Å., and suggest that the structure of CsCuCl_3 also consists essentially of six close-packed (CsCl_3) layers of the type shown in Fig. 1. In the investigation of $\text{Cs}_3\text{Ti}_2\text{Cl}_9$ it was found that lamellar twinning, leading to a higher apparent symmetry, usually occurred. Crystals of CsCuCl_3 were therefore grown both very rapidly and very slowly, and their X-ray photographs compared. No differences were detected, and it was assumed that twinning of the type encountered in the thallium compound was not occurring in this compound. In $\text{Cs}_3\text{Ti}_2\text{Cl}_9$ the thallium atoms are arranged in pairs of adjacent octahedral holes between the close-packed layers. Since an octahedral environment of 6 Cl (at about 2.5 Å.) would not be unreasonable for copper, it was decided first to try all the possible arrangements of copper atoms in octahedral

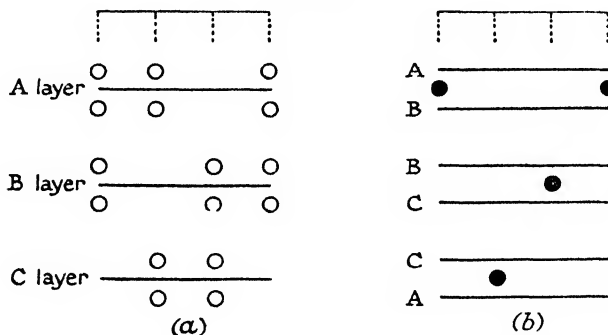
holes. For any structure consisting of six close-packed layers, which contain all the Cs and Cl atoms, the orders of 000 l with $l \neq 6n$ will occur only (1) if the layers are displaced from their ideal heights, $c/6$ apart, or (2) if the Cu atoms are placed in such positions as to contribute to these orders. The survey of possible structures based on octahedrally co-ordinated copper was therefore not restricted to those containing 6_1 (or 6_2) axes, but was carried out in the most exhaustive way in order to eliminate such structures conclusively.

FIG. 1.

Close-packed $CsCl_3$ layer (caesium ions represented by shaded circles).

The problem is to determine the possible structures built of six close-packed layers, each of composition $CsCl_3$, held together by 6 Cu placed in octahedral holes between sets of 3 Cl in adjacent layers. Adopting the conventional nomenclature, each layer may be an A, B, or C layer (*i.e.*, the Cs is at $\frac{1}{3}, \frac{2}{3}$ or 00), with the provisos that similar layers may not be adjacent, and the repeat unit along the c axis must not exceed 6 layers. It is necessary to place one Cu between each pair of layers, for the following reason. The possible positions for Cu atoms lie on the lines 00 z , $\frac{1}{3}z$ or $\frac{2}{3}z$, but on either side of a layer of a given type only two of these positions are possible. Representing the long diagonal of the base of the unit cell (the broken line in Fig. 1) as a horizontal line, we may indicate these possibilities as in Fig. 2*a*, so that between

FIG. 2.

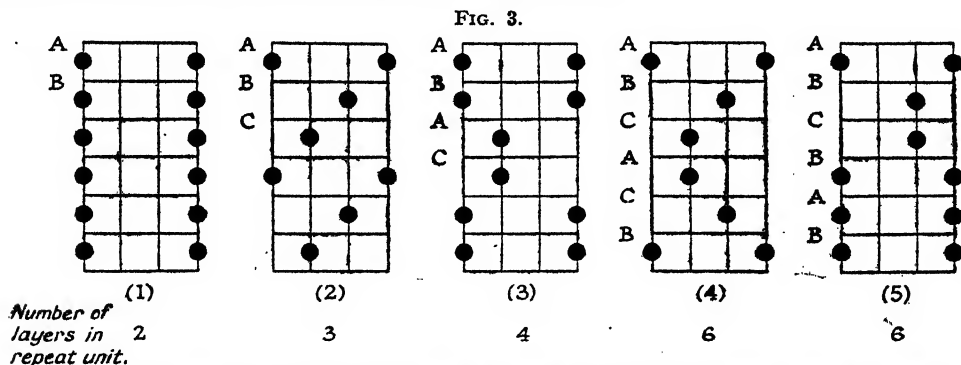


Possible positions of Cu atoms : (a) on either side of an A, B, or C layer ; (b) between AB, BC, or CA layers.

layers AB, BC, CA the only possible positions for Cu are those shown at (b), Fig. 2. The various sequences of layers lead to five possible structures. These are summarised diagrammatically in Fig. 3 as elevations on (11 $\bar{2}$ 0) of one unit cell.

If a layer is represented by h when the two surrounding layers are of the same type, and by c if they are of different types, then the sequences of close-packed layers in these structures are (1) h , (2) c , (3) hc , (4) hcc , (5) $h h h c h c$. Of these the first four are well known as the four simplest types of close-packing. In the first two, hexagonal and cubic close-packing respectively, all the spheres are equivalent; in the second two there are two kinds of non-equivalent spheres. The fifth structure is of a more complex type, and contains four kinds of non-equivalent spheres—

it is interesting as the only one of the six-term set with a repeat unit of only six layers.* In structure (1) there are infinite chains of octahedra formed by sharing opposite faces. Structure (2) is the perovskite structure. The only structures to be tested are (4) and (5), both of which contain infinite 3-dimensional $(\text{MX}_6)_n$ ions formed by MX_6 octahedra sharing all their X atoms with other octahedra. The mode of linking of the octahedra is discussed later. Both these structures can be built up to conform to the space-group $C6m2$, but a comparison of intensities calculated on the basis of either of these structures with those observed for CsCuCl_3 shows that neither is the structure of this compound. In $C6m2$ the only variable x parameters are those of the chlorine atoms, and no small modification of the ideal structures could possibly account for the observed intensities. For example, they both give $F_{600} = F_{006}$ and $F_{601} = 0$, whereas 600 is quite weak and $601 > 600$. It is therefore concluded that CsCuCl_3 does not possess a structure in which Cu is octahedrally co-ordinated by six chlorine atoms.



Possible structures for a complex halide CsMCl_3 , assuming octahedral co-ordination of M atoms (diagrammatic).

To account for the general nature of the $h00$ and $hk0$ intensities it is necessary to shift the close-packed layers relative to one another. Starting with structure (1), with hexagonal close-packing of $(\text{Cs} + 3\text{Cl})$ and Cu atoms with six octahedral neighbours at about 2.5 Å., it is possible by suitable translations of the layers relative to one another to give each Cu four nearest Cl neighbours at about 2.3 Å. and two more distant neighbours. The relation between a pair of adjacent layers is that shown in Fig. 4. In order to fit this new arrangement into the space-group $C6_2$ the three chlorine atoms in any layer are no longer equivalent, and the centre of the (distorted) octahedron of chlorine atoms now lies off the line $00z$. The Cu atoms are therefore arranged around the screw axis in a spiral arrangement. Slight movements from the positions in the ideal close-packed layer of Fig. 1 were necessary to improve the agreement between observed and calculated intensities, and the following parameters were finally chosen as giving the best overall agreement:

Cu: $6(a)$, $x00$, etc., $x = 0.07$

Cs: $6(b)$, $x, 2x, \frac{1}{2}$, etc., $x = 0.345$

Cl_1 : $6(b)$, $x, 2x, \frac{1}{2}$, etc., $x = 0.90$

Cl_2 : $12(c)$, xyz , etc., $x = 0.35, y = 0.22, z = 0.25$

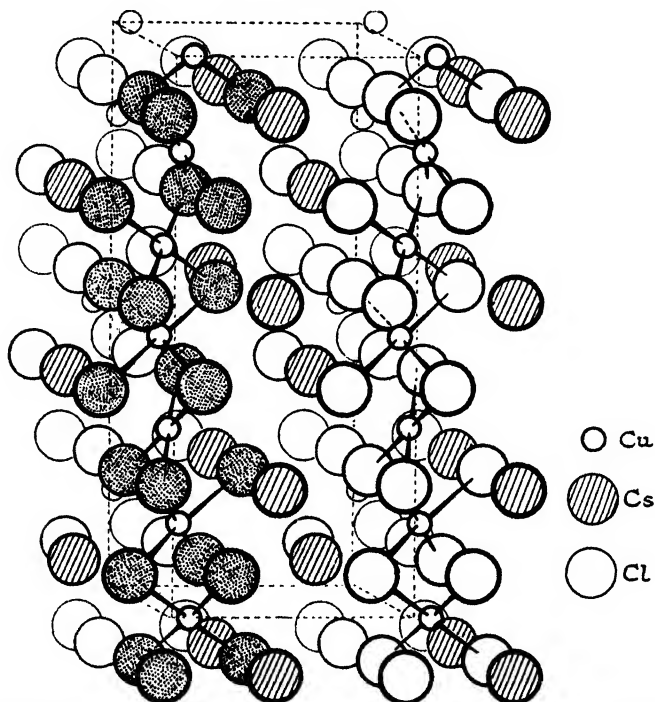
* The simplest close-packed arrangements are tabulated below, together with the numbers of layers in a repeat unit. Certain of these, containing only two types of non-equivalent atom, have recently been discussed by Hägg (*Arkiv Kemi, Min. Geol.*, 1942, **18**, B, No. 3), in connection with the structures of the cadmium halides.

Symbol.	No. of layers in repeat unit.	Symbol.	No. of layers in repeat unit.
h	2	$hhccc$	5
c	3	$hhcc$	10
hc	4	$hchch$	10
hcc	6	$hcccc$	10
chh	9	$chchc$	15
$hhhc$	8	$hhhhc$	15
$ccch$	8	$hhchc$	6
$cchh$	12	$hhhhc$	12
		$hcccc$	12
		$hhccc$	12
		$hhccc$	12
		$hhccc$	18
		$hhccc$	18
		$ccchh$	18

in a structure in which the bonds differ appreciably in amount of ionic character. Absorption of Cu-K_α radiation by this crystal is appreciable, necessitating the use of a very small equidimensional crystal. A temperature factor has not been incorporated into the calculated intensities, nor has allowance been made for absorption, the effect of which may be appreciable for some reflexions.

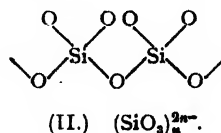
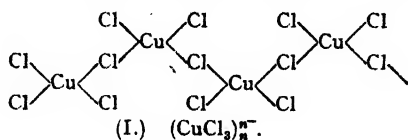
Description of the Structure.—The structure, which is illustrated in Fig. 5, consists essentially of close-packed layers of composition $(\text{CsCl}_3)_n$, arranged approximately in hexagonal close-packing, with the copper atoms between the layers surrounded by four chlorine atoms in a square planar configuration. The next nearest neighbours of a copper atom are two more chlorine atoms,

FIG. 5.

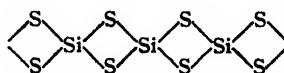
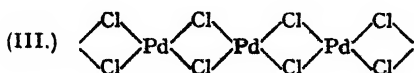


Unit cell of the crystal structure of CsCuCl_3 . The stippled circles represent chlorine atoms forming part of one $(\text{CuCl}_3)_n^{2n-}$ ion.

forming with the other four a somewhat distorted octahedron. The square CuCl_4 groups are arranged in a spiral around six-fold screw axes and are joined up, by sharing two adjacent corners, to form infinite chains of composition $(\text{CuCl}_3)_n^{2n-}$. The structure may therefore be regarded alternatively as consisting of infinite chain ions $(\text{CuCl}_3)_n^{2n-}$ held together laterally by Cs^+ ions. This chain ion (I) is the analogue, for 4-square co-ordination, of the $(\text{SiO}_3)_n^{2n-}$ ion in diopside (II), in which tetrahedral SiO_4 groups are joined up by sharing corners. The infinite



linear molecules in PdCl_2 , formed by planar PdCl_2 groups sharing opposite edges, are related in a similar way to the infinite chain molecules in SiS_2 , which contains tetrahedral SiS_4 units (III).



From the parameters given above the following interatomic distances are calculated :

Cu :	{ 2 Cl at 2.30 Å.	Cs :	6 Cl in same close-packed plane 3.40—3.82 Å.; mean, 3.64 Å.
	2 Cl at 2.27 Å.		4 Cl in adjacent planes, 3.56—3.69 Å.; mean, 3.63 Å.
	2 Cl at 2.65 Å.		2 Cl in adjacent planes, 4.13 Å.

The Cu—Cl bond length is, to within the probable accuracy, the same as that found in $K_2CuCl_4 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$.

Discussion.—The adoption of this structure by $CsCuCl_3$ emphasises the point made in the introduction, that in its crystalline compounds bivalent copper tends to resemble Pd^{II} rather than the elements Co, Ni, or Zn. It has been shown that there are several possible structures for $CsCuCl_3$ containing 6-co-ordinated cupric ions with Cu—Cl about 2.5 Å., with an equally satisfactory packing of Cs^+ and Cl^- ions. In preference to these, however, $CsCuCl_3$ adopts a structure with a distorted Cs—Cl packing in order that the copper atoms shall have only four nearest neighbours arranged at the corners of a square.

It is worth while considering briefly the general nature of the structures shown in Fig. 3, as this is of interest in connexion with the stability of complex halides $CsMCl_3$. In the perovskite structure, ABX_3 , every BX_6 octahedron shares its corners with 6 other such octahedra, while in structure (1), Fig. 3, the octahedra are joined together into chains by sharing opposite faces. This type of complex ion has so far not been found, and may well be unstable owing to the close approach of the two B atoms. The linking of such octahedral co-ordination groups by sharing faces is not known to proceed beyond the formation of the ion $(B_2X_9)^-$, in $Cs_3Ti_2Cl_9$, etc. In such an ion the repulsion of the B atoms does lead to some distortion of the BX_6 octahedra, a type of distortion which is not possible if the linking of octahedra proceeds further. The remaining three structures in Fig. 3, viz., (3), (4), and (5), are, as regards the mode of linking of the BX_6 octahedra, intermediate in nature between structures (1) and (2). In structure (3) all the BX_6 octahedra are equivalent and share three corners with other octahedra and the remaining three (a face) with a fourth octahedron. In structures (4) and (5), however, the BX_6 octahedra are no longer all equivalent. In (4), two-thirds share a face and three corners, one-third six corners, while in (5) two-thirds share a face and three corners and the remainder two faces. It seems probable, therefore, that all the structures (1), (3), (4), and (5) in Fig. 3 would be less stable than (2), the perovskite structure, so that we should expect halides KMF_3 or $CsMCl_3$ containing octahedrally co-ordinated atoms, if they are formed at all, to have that structure. Now, although the simple halides MCl_2 of Fe, Co, Ni, and Zn all crystallise with a structure in which the metal atom is surrounded by six chlorine atom at about 2.5 Å., stable complex halides $CsMCl_3$ are rare. Moreover, in the complex halides they do form they exhibit, in the compounds so far studied, a lower co-ordination number than in the simple halide. (It should be remarked that cadmium behaves differently from the above elements and retains 6-co-ordination in its complex halides, which are therefore different structurally, and also often in formula type, from those of Fe^{II} , Co, Ni, and Zn.)

TABLE II.
Complex chlorides of the type $A_mBCl_n \cdot xH_2O$.

Co-ordination of B by Cl.	Fe^{II} , ?	Co^{II} , 4, tetra- hedral. ¹	Ni, ?	Cu^{II} , 4, planar. ²	Zn, 4, tetra- hedral. ³	Cd, 6, octa- hedral. ⁴
n.						
Na	None	None	?	None	?	?
K	3 $KFeCl_3 \cdot 2H_2O$	None	$KNiCl_3 \cdot 5H_2O$	$KCuCl_3$	$KZnCl_3 \cdot 2H_2O$	$KCdCl_3 \cdot H_2O$
	4 $K_2FeCl_4 \cdot 2H_2O$	—	—	$K_2CuCl_4 \cdot 2H_2O$	K_2ZnCl_4 (and $2H_2O$)	K_2CdCl_4
	5 —	—	—	—	—	[n = 6 : K_4CdCl_6]
Rb	3 ?	$RbCoCl_3 \cdot 2H_2O$?	?	?	$RbCdCl_3$
	4 —	$Rb_2CoCl_4 \cdot 2H_2O$	—	—	—	Rb_2CdCl_4
	5 —	—	—	—	—	[n = 6 : Rb_4CdCl_6]
Cs	3 $CsFeCl_3 \cdot 2H_2O$	$CsCoCl_3 \cdot 2H_2O$	$CsNiCl_3$	$CsCuCl_3$	—	$CsCdCl_3$
	4 $Cs_2FeCl_4 \cdot 2H_2O$	Cs_2CoCl_4	—	Cs_2CuCl_4	Cs_2ZnCl_4	Cs_2CdCl_4
	5 —	Cs_3CoCl_5	—	—	Cs_3ZnCl_5	—

¹ Established in Cs_2CoCl_4 (Powell and Wells, *J.*, 1935, 359).

² Established in $CsCuCl_3$.

³ Established in $(NH_4)_2ZnCl_4$ (Klug and Alexander, *J. Amer. Chem. Soc.*, 1944, 66, 1056).

⁴ Established in $RbCdCl_3$ (MacGillavry, Nijveld, Dierdorp, and Karsten, *Rec. Trav. chim.*, 1939, 58, 193).

Table II gives a general, though rather incomplete, picture of the types of complex chloride formed by these elements which can be isolated from aqueous solution at 25°. Of the elements Fe^{II} , Co, Ni, and Zn, apparently only Ni forms a halide of the type CsMCl_3 (Campbell, *Amer. J. Sci.*, 1894, 48, 418; *Z. anorg. Chem.*, 1895, 8, 126). The salt CsNiCl_3 is obtained by evaporating a concentrated solution containing 12 CsCl : 1 NiCl_2 , and it is immediately decomposed by water. Its structure is not known. In the case of iron and cobalt, the dihydrates are obtained. It would seem that the compounds CsFeCl_3 , etc., are on the borderline as regards stability towards water, and that while CsNiCl_3 can just be prepared from aqueous solution in the presence of a very large excess of CsCl , the others take up $2\text{H}_2\text{O}$, presumably between the chains as in $\text{K}_2\text{SnCl}_4 \cdot \text{H}_2\text{O}$. With the smaller rubidium and potassium ions hydration is more frequent and often occurs also in the salts $\text{M}_2\text{FeCl}_4 \cdot 2\text{H}_2\text{O}$, etc., while sodium salts are in general not obtainable at all. This effect is well illustrated by the complex caesium-cobalt chlorides (see Table II) and by the alkali-copper halides:

Cs.	Rb	K.	Na.	Li.
CsCuCl_3	?	KCuCl_3	—	$\text{LiCuCl}_3 \cdot 2\text{H}_2\text{O}$
Cs_2CuCl_4	—	—	None	—
$(\text{Cs}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O})$	—	$\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$	—	—

Whereas CsCuCl_3 is a stable salt, KCuCl_3 is unstable in moist air, decomposing to a mixture of two hydrated salts ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$), and KCuBr_2 is very hygroscopic. The appearance of a hydrated lithium salt, in contrast to the non-existence of sodium salts, is presumably due to the fact that an entirely different type of structure becomes possible for the very small, tetrahedrally co-ordinated lithium ion. Similar variations in degree of hydration and stability towards water are found in many other series of complex halides, e.g., the dichloriodides, hexachloroplatinates, etc.

This question, why certain compounds are formed by one element and not by others, is obviously of great interest in chemistry. The direct approach would involve the calculation of the lattice energies of all possible structures for the hypothetical compound, but this exhaustive treatment is not likely to be possible in many cases. In general, it is not possible even to deduce all the reasonable structures for a given compound, so that in the most favourable cases we should only be able to say that one or more specified structures would be unstable, without being sure that there are no other structures the compound could adopt.

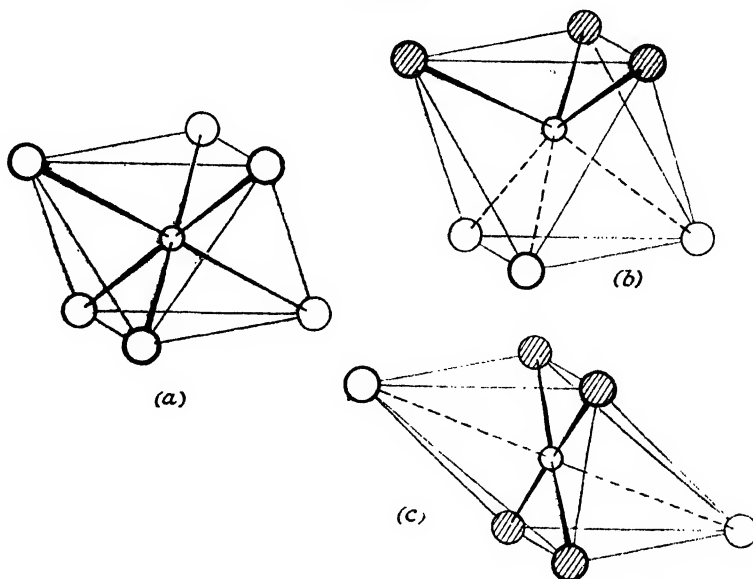
In the case of halides CsMCl_3 (where $\text{M} = \text{Mn, Fe, Co, Ni}$) it would seem that the perovskite structure should be the most stable, it being assumed (1) that the Cs and Cl will be essentially close-packed, and (2) that structures of the type adopted by the larger Cd, containing "band" ions $(\text{CdCl}_3)_n^{2-}$, are not possible for these elements. The instability of these compounds would therefore suggest that the perovskite structure, with linear M-Cl-M bonds, is not stable for chlorides. [It has been stated that CsCdCl_3 (Ferrari and Baroni, *Atti R. Accad. Lincei*, 1927, 6, 418) and CsHgCl_3 (Natta, *ibid.*, 1927, 5, 1003) crystallise with this structure, though the compounds were not studied in any detail. A regular octahedral arrangement of 6 Cl around Hg would be very surprising, but unfortunately the precise location of the relatively light Cl atoms would in any case be very difficult.] The fact that the simple halides MnCl_2 , etc., have the CdCl_2 structure with octahedral co-ordination of the metal atoms shows that it is not the requirement of 6-co-ordination which prevents the complex halides adopting the perovskite structure, but it is significant that in the CdCl_2 structure the chlorine bonds are non-linear. In complex oxides the ideal perovskite structure (with linear -O- bonds) is by no means as common as was once thought (Megaw, *Proc. Physical Soc.*, 1946, 58, 133). We conclude therefore that the instability of these halides CsMCl_3 is due to the fact that the perovskite structure is stable only for the essentially ionic fluorides and oxides of the more electropositive elements. For chlorides it is far less stable than for fluorides, so that instead of CsCoCl_3 we find $\text{CsCoCl}_3 \cdot 2\text{H}_2\text{O}$, with presumably either infinite chain ions $(\text{CoCl}_3)_n^{2-}$, containing tetrahedrally co-ordinated cobalt and H_2O molecules between the chains, or (less probably) infinite aquo-ions or bands as in NH_4CdCl_3 with H_2O between the "band" ions.

The structures of complex halides ABX_3 , in which the ratio of halogen to alkali-metal atoms is 3 : 1 are of special interest because for this ratio the X and A atoms together can form a close-packed array, provided they are of about the same size. The conditions for forming such structures are particularly favourable for K and F and for Cs and Cl, so that in all the following compounds the alkali and halogen atoms are close-packed:



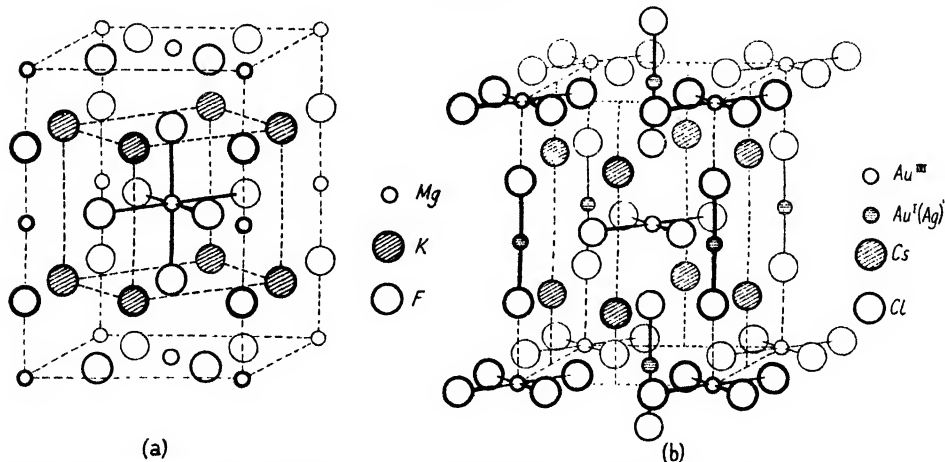
From the geometrical standpoint, the structures of $KMgF_3$, K_2SiF_6 , and $Cs_3Ti_2Cl_9$ differ only in the proportions and arrangement of octahedral holes which are occupied by the more highly charged positive ions, leading in the last two cases to finite $(SiF_6)^{4-}$ and $(Ti_2Cl_9)^{3-}$ ions respectively. In the perovskite structure of $KMgF_3$ no discrete complex ions exist; it is to be regarded as an

FIG. 6.



Two modes of distortion of an octahedral co-ordination group BX_6 , (a), to give (b) a pyramidal molecule BX_5 , and (c) a planar BX_4 group.

FIG. 7.

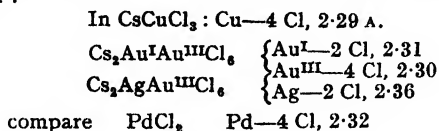


(a) The perovskite structure of $KMgF_3$, with octahedral MgF_6 co-ordination groups; (b) the structure of $Cs_2Au^I Au^{III} Cl_6$ with linear $Au^I Cl_2$ and planar $Au^{III} Cl_4$ groups.

infinite 3-dimensional array of K^+ , Mg^{2+} and F^- ions. For atoms which do not form six octahedral bonds these simple close-packed structures are not possible, and we find interesting variants for $Cs_2As_2Cl_9$ (Hoard and Goldstein, *J. Chem. Physics*, 1935, 3, 117), $CsCuCl_3$, and $CsAuCl_3$. These illustrate three different ways of distorting an octahedral co-ordination group to give less than six nearest neighbours (Figs. 6 and 7), viz., 3 pyramidal (in $Cs_2As_2Cl_9$), 4 planar (in $CsCuCl_3$), and 4-planar or 2 linear neighbours (in $Cs_2Au^I Au^{III} Cl_6$). In $CsCuCl_3$ all the Cu^{II}

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atoms are equivalent and are surrounded by 4 Cl in a plane. The gold compound, although having a similar empirical formula, is of a different kind, containing Au^{I} and Au^{III} atoms in equal numbers. Just as CsCuCl_4 adopts a distorted version of an idealised hexagonal close-packed structure, so the gold compound has a distorted version of the perovskite structure (Elliott and Pauling, *J. Amer. Chem. Soc.*, 1938, 60, 1846). The distortion is of such a nature as to give Au^{I} two nearest neighbours (linear Au^{I} bonds) and Au^{III} four nearest neighbours (4 square Au^{III} bonds), as shown in Fig. 7, (a) and (b). The mixed halide $\text{Cs}_2\text{AgAu}^{\text{III}}\text{Cl}_6$ has the same structure. The bond lengths in the (CuCl_4) , $(\text{Au}^{\text{I}}\text{Cl}_2)$, $(\text{Au}^{\text{III}}\text{Cl}_4)$, and (AgCl_2) groups in these closely related structure are very similar :



We may summarise the crystal chemistry of these complex halides in the scheme below.

Crystal structures of complex halides ABX_3 with close-packed A and X atoms.

			<i>Distorted perovskite structure.</i>
	BX_6 regular octahedral co-ordination	$\text{Cs}_2\text{Au}^{\text{I}}\text{Au}^{\text{III}}\text{Cl}_6$	$\left\{ \begin{array}{l} \text{Au}^{\text{I}}\text{Cl}_2 \text{ linear} \\ \text{Au}^{\text{III}}\text{Cl}_4 \text{ planar.} \end{array} \right.$
Cubic close-packing	K_2SiF_6 structure Perovskite structure KMgF_3		BX_3 pyramidal $\text{Cs}_3\text{As}_2\text{Cl}_7$ structure
	Fig. 3, structures (3), (4), (5)		
(More complex types of close-packing)	intermediate between perovskite structure and structure (1), below		
Hexagonal close-packing	Structure (1), Fig. 3	BX_6 octahedral but slightly distorted owing to formation of B_2X_9 ion $\text{Cs}_3\text{W}_2\text{Cl}_9$ structure $\text{Cs}_3\text{Tl}_2\text{Cl}_9$ structure	BX_4 planar CsCuCl_3 structure

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[Received, February 15th, 1947.]

333. The Crystal Structure of Anhydrous Cupric Chloride, and the Stereochemistry of the Cupric Atom.

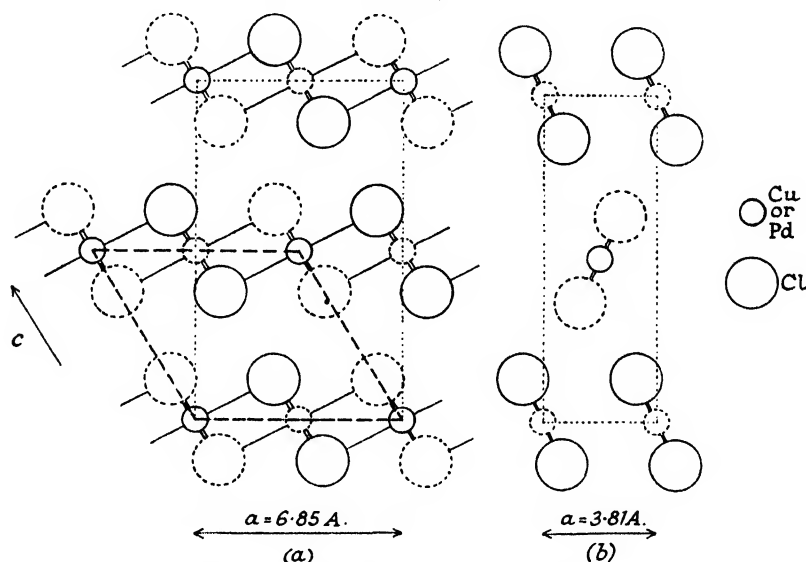
By A. F. WELLS.

Anhydrous cupric chloride is monoclinic: $a = 6.85$, $b = 3.30$, $c = 6.70 \text{ \AA.}$, $\beta = 121^\circ$; space-group C2/m , with Cu at 000, $\frac{1}{2}\frac{1}{2}0$, and 4 Cl at $x0z$, etc., $x \approx \frac{1}{2}$, $z \approx \frac{1}{2}$. The structure contains infinite chain molecules formed by planar CuCl_4 groups sharing opposite edges, as in PdCl_2 . The packing of these chains is different from that found in PdCl_2 , apparently in order to give Cu^{II} two next nearest neighbours at about 3 Å. completing a distorted octahedral co-ordination group. The stereochemistry of the cupric atom is discussed.

CUPRIC chloride is one of the few halides of the commoner elements which has not previously been studied by the methods of X-ray crystallography. Its structure is of interest in view of the planar configuration of four bonds from a cupric atom, already established in a number of crystalline salts and co-ordination compounds. Since the length of a $\text{Cu}^{\text{II}}-\text{Cl}$ bond is the same ($2.30 \pm 0.03 \text{ \AA.}$) as that of $\text{Pd}^{\text{II}}-\text{Cl}$, one might expect cupric chloride to have the same crystal structure as palladous chloride (Wells, *Z. Krist.*, 1938, 100, 189), in which planar PdCl_4 groups are joined up by sharing opposite edges to form infinite chain molecules. In fact, it is found that the structure of CuCl_2 , although closely related to that of PdCl_2 , differs from that structure in a significant way. This point will be discussed later in more detail in a survey of the crystal structures of certain cupric compounds.

Determination of the Crystal Structure of Cupric Chloride.—Cupric chloride is hygroscopic, and is normally obtained from aqueous solution as the dihydrate. The anhydrous salt is readily prepared by heating the dihydrate to a moderate temperature in a stream of hydrogen chloride, being obtained as brown pseudomorphs of the needles of the blue dihydrate. This material is very poorly crystalline, as judged by its powder photograph, and attempts to index the latter unambiguously were not successful. Single crystals of cupric chloride were therefore prepared by melting this material in a hard-glass tube (when some decomposition takes place), allowing it to cool, and breaking up the cooled melt. The crystals are sufficiently stable on a dry day to permit microscopic examination and the selection of suitable crystals which can then be sealed up in short lengths of thin-walled capillary tube. The crystals are thin laths (001) or needles, elongated along the b axis. There is perfect (001) cleavage, and moreover, the slightest pressure on a (001) plate causes it to split along its length (b) into a bundle of fibres, looking much like asbestos. By reflected light the crystals appear brown. They exhibit striking pleochroism, the light transmitted being yellowish-green for vibrations perpendicular to b and reddish-brown

FIG. 1.



Projections of the crystal structures of (a) CuCl_2 and (b) PdCl_2 on (010), showing the differences in packing of the chains. Atoms at $y = 0$ and $y = \frac{1}{2}$ are represented by full and dotted circles respectively. In (a) the broken lines enclose the monoclinic unit cell, and the dotted lines indicate the pseudo-rhombic cell.

for vibrations along b , a colour change quite similar to that of CsCuCl_3 (preceding paper). X-Ray examination (Cu-K_α radiation) shows the crystals to be monoclinic: $a = 6.85$, $b = 3.30$, $c = 6.70$ Å., $\beta = 121^\circ$. Owing to the physical weakness of the crystals, which are easily bent and split, the accuracy of these figures is probably no greater than $\pm 1\%$. The density was not determined, but since by analogy with the structure of PdCl_2 the above cell contains 2 CuCl_2 , the calculated density is 3.44 g./c.c.

The halvings observed are those characteristic of a c face-centred lattice. Since there is no evidence of lower symmetry the space-group is assumed to be $C2/m$. The strong absorption of light vibrating along b and the fact that the length of the b axis is the same as for PdCl_2 suggest a chain structure closely related to that of PdCl_2 . In fact it is found that the photographs about the b axis can be indexed on the basis of a pseudo-rhombic all face-centred cell with dimensions: $a = 6.85$, $b = 3.30$, $c = 11.4$ Å., containing 4 CuCl_2 . The spacings of the $h0l$ planes show also that the projection of the structure on (010) is pseudo-hexagonal. The cell dimensions of PdCl_2 (orthorhombic, space-group $Pnmm$) are: $a = 3.81$, $b = 3.34$, $c = 11.0$ Å., i.e., very similar to those of CuCl_2 except that the a axis is nearly doubled in the case of the latter. This increased a dimension is clearly due to the interposition of a chain related by a translation of $b/2 + a/2$ between alternate chains along the a axis. Since the lattice is known to be c face-centred monoclinic, the only possible way of packing the chains is that shown in Fig. 1(a),

the chain length (b) being normal to the plane of the paper. The corresponding projection of the structure of PdCl_2 is shown in Fig. 1(b). It will be seen that this way of packing the CuCl_2 chains accounts for the pseudo-hexagonal nature of the b axis and for the pseudo-rhombic all face-centred unit cell corresponding to the true orthorhombic cell of the palladium compound.

Considerations of packing show that the planes of the CuCl_2 groups must lie approximately in (100). The structure is then defined as follows, the space-group nomenclature of the International Tables being used:

Cu in 2 (a): 000, $\frac{1}{2}\frac{1}{2}0$

Cl in 4 (i): $x0z$, etc., $x \approx \frac{1}{2}$, $z \approx \frac{1}{2}$

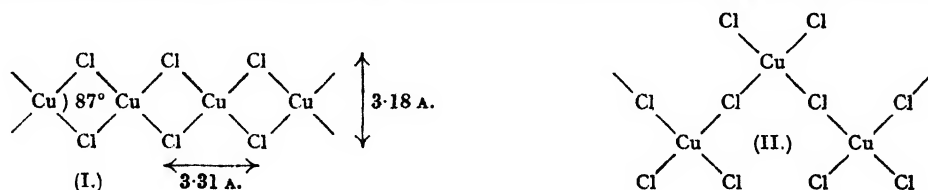
Owing to the fact that the parameters x and z have, at least approximately, the special values $\frac{1}{2}$ and $\frac{1}{2}$ respectively, striking intensity relationships are observed, for all the structure factors have one of the three values, $2f_{\text{Cu}}$, $2f_{\text{Cu}} + 4f_{\text{Cl}}$ or $2f_{\text{Cu}} - 4f_{\text{Cl}}$. Because of the small size of the unit cell, comparatively few reflexions are observed for copper radiation, and the only practicable way of determining the parameters accurately would be to project the structure on (010), using a shorter radiation and, if possible, avoiding the use of a capillary tube. Since it is not likely that better intensity data will be obtainable in the near future, it was considered desirable to publish the present paper as this establishes the structure within close limits and raises an interesting point about the stereochemistry of the cupric atom.

The calculated and observed intensities given in Table I are sufficient to prove the essential correctness of the structure. The intensities are calculated as proportional to $F^2(1 + \cos^2 2\theta/2 \sin 2\theta)$ the f -curves used being those for Cu and Cl atoms given in the International Tables (Vol. II). The planes are arranged in order of increasing $\sin \theta$, and include only those with $h = 0$ or 1.

TABLE I.

hkl	I , calc.	I , obs.	hkl	I , calc.	I , obs.	hkl	I , calc.	I , obs.
001	202	vs	312	112	s	314	0	—
201	97	s	112	106	s	113	11	w
200	309	vs	113	26	w	114	0	—
202	0	—	402	0	—	004	45	ms
110	0	—	310	0	—	203	10	w
111	74	s	313	22	w	205	10	w
002	0	—	202	0	—	401	10	w
111	44	ms	204	87	ms	405	10	w
112	185	vs	401	20	w	512	39	m
201	40	m	403	20	w	513	10	w
203	40	m	400	47	ms	312	38	m
003	30	mw	404	47	ms	315	9	w
311	27	w	311	11	w			

Description of the Structure.—The structure is illustrated in Fig. 2, which shows three unit cells. The Cu and Cl atoms are joined together to form infinite chains in which each Cu is surrounded by 4 Cl in a plane and each Cl is attached to 2 Cu. From the similarity in the lengths of the b axes in CuCl_2 and PdCl_2 it may be concluded that the structure of a chain is very similar to that in PdCl_2 , viz., (I), though this small distortion of the CuCl_2 groups has not been

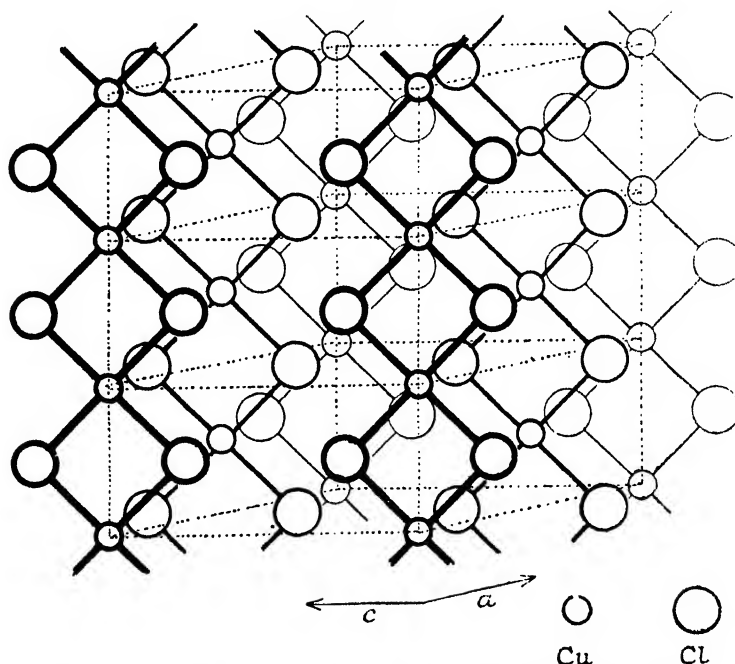


established in the present case. The length of the Cu-Cl bond is the same (2.3 Å.) as that in CsCuCl_2 , $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$, and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$. It has been shown (preceding paper) that in CsCuCl_2 exactly similar planar CuCl_2 groups are joined together to form infinite chain ions of the type (II). The configuration of the CuCl_2 chain being assumed to be that shown above, the shortest distance between chlorine atoms of different chains is 3.5 Å. The next nearest neighbours of a copper atom are two more Cl (in adjacent chains related by the c face-centring) at 2.95 ± 0.05 Å. These weak Cu-Cl bonds, discussed below, are shown as light full lines in Fig. 1(a), and they complete the distorted octahedral arrangement of six bonds from each Cu atom. Taking account of this weak additional binding, the chains form sheets parallel to (001), though, of course, by

far the strongest bonds are those within the individual chains, which run parallel to [010]. A somewhat analogous state of affairs is found in the structure of mercuric bromide (Verweel and Bijvoet, *Z. Krist.*, 1931, **77**, 122), in crystals of which each Hg atom has a distorted octahedral environment, with two of the six Br much closer than the other four. Having regard only to the strongest bonds, the structure contains linear molecules HgBr_2 , but taking into account also the weak secondary bonds from a Hg atom to its four next nearest neighbours, the structure is seen to be a layer structure. In PdCl_2 , on the other hand, there is no such suggestion of secondary bonds linking the chains laterally into layers, and the mode of packing of the infinite chains is much more like that of non-polar chain molecules such as long-chain hydrocarbons.

The structure clearly accounts for the strong absorption of light vibrating along the b axis, this being the direction of the infinite chain molecules. The structure also explains the perfect (001) cleavage, and the remarkable tendency to split into fibres is obviously due to the secondary cleavage parallel to (100). The X -ray photographs of some crystals show additional reflexions

FIG. 2.



The crystal structure of anhydrous cupric chloride (three unit cells).

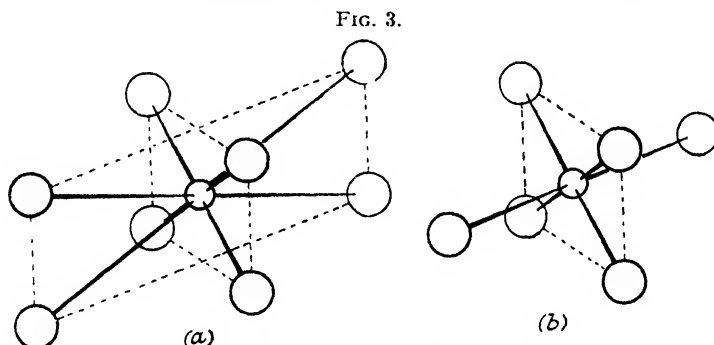
due to twinning, the possibilities of which are considerable. Rotational twinning (about b) is possible because of the pseudo-hexagonal packing of the chains. Also, if the set of chains shown (in projection) in the lower part of Fig. 1(a) is sheared in the direction of the a axis in the plane (001), they can rearrange by sliding over one another to take up the alternative orientation related to the first by reflexion across the plane (201).

The Stereochemistry of the Cupric Atom.—Perhaps the most interesting result of this study is the demonstration that the structure of CuCl_2 is different from that of PdCl_2 . It was known previously that the lengths of the $\text{Cu}^{\text{II}}\text{-Cl}$ and the $\text{Pd}^{\text{II}}\text{-Cl}$ bonds are the same to within the accuracy to which they are known, and the present work confirms this. Both compounds form exactly the same type of infinite chain molecule, yet the chains are packed in different ways in the crystals of CuCl_2 and PdCl_2 . It is worth while enquiring why this should be so. In PdCl_2 , the next nearest chlorine neighbours of a Pd atom (*i.e.*, after the four coplanar neighbours) are four more (at 3.85 Å.) arranged at the corners of a rectangle, the plane of which is perpendicular to that of the PdCl_4 group [see Fig. 3(a)]. In CuCl_2 , on the other hand, neighbouring chains along [100] are displaced relative to one another in such a way that the next nearest neighbours of a Cu atom are two more Cl atoms of neighbouring chains. These complete a distorted octahedron of Cl atoms around the Cu atom [Fig. 3(b)], and they are at a distance of only about

2.95 Å. It might appear fanciful to suppose that the different packing of the chains is adopted in order to give Cu^{II} this distorted octahedral environment, particularly as it is at present difficult to say what type of binding a bond of this length would indicate, were it not for the fact that Cu^{II} has precisely this environment in a number of other crystalline salts. The structures (and stabilities) of certain crystalline cupric salts present a number of striking features to which attention does not appear to have been drawn. The facts are as follows.

(1) *Potassium cupric halides.* The only potassium cupric halide stable in the presence of water at ordinary temperatures is the blue-green hydrated salt $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$. (The red KCuCl_3 can be prepared from concentrated solution but is rapidly converted by moist air into a mixture of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$.) Palladous chloride on the other hand forms the stable anhydrous K_2PdCl_4 . In crystalline K_2PdCl_4 the PdCl_4^{2-} ions are stacked vertically above one another, so that the next nearest Cl neighbours of a Pd atom (apart from those of other PdCl_4^{2-} ions coplanar with the one under consideration) are 8 Cl at distances of more than 4 Å. In contrast to this, $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$ does not contain planar CuCl_4^{2-} ions at all, but each Cu has, as nearest neighbours, 2 O (of H_2O) at 1.97 Å., 2 Cl at 2.32 Å., and 2 more Cl at 2.95 Å., the whole set forming a distorted octahedral group around the Cu (Chrobak, *Z. Krist.*, 1934, 88, 35; "Strukturbericht", 1936, 4, 104). In $\text{Pd}(\text{NH}_3)_4\text{Cl}_2 \cdot \text{H}_2\text{O}$ we find Pd with 4 NH_3 as nearest neighbours at 2.02 Å., with 8 Cl as next nearest neighbours, arranged at the corners of a cube, at 4.27 Å. (Dickinson, *Z. Krist.*, 1934, 88, 281).

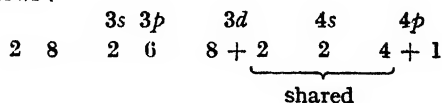
(2) *Cupric chloride dihydrate.* Here again we might have expected to find 4 Cl around Cu at about 2.30 Å. Instead, we find exactly the same arrangement of atoms as in $\text{K}_2\text{CuCl}_4 \cdot 2\text{H}_2\text{O}$,



The environment of (a) Pd in PdCl_4 and (b) Cu in CuCl_2 (small circles represent metal atoms).

viz., 2 O at 2.01 Å., 2 Cl at 2.31 Å., and 2 Cl at 2.98 Å. (Harker, *ibid.*, 1936, 93, 136). It may be argued that the displacement of two of the four possible chlorine atoms by 2 H_2O (to give 2 H_2O and 2 Cl as nearest neighbours instead of 4 Cl) is connected with the strong tendency of Cu^{II} to form bonds to oxygen—witness the numerous "basic" salts of copper (actually hydroxy-salts)—but this does not account for the persistent 4 + 2 co-ordination of Cu^{II} which also occurs in anhydrous CuCl_2 and CsCuCl_3 . The comparison of the stereochemistry of Cu^{II} and of Pd^{II} will be more complete when two more structures are known, those of $\text{PdCl}_2 \cdot 2\text{H}_2\text{O}$ and Cs_2CuCl_4 . It will be interesting to know whether the former adopts the same structure as $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ or whether, as seems more likely, Pd will retain 4 Cl as its immediate neighbours. A knowledge of the structure of the latter salt (or some similar compound) is required because the existence of discrete CuCl_4^{2-} ions has not so far been proved in any crystal.

The above considerations suggest that the statement that Cu^{II} forms four coplanar bonds may require modification, in the sense that the analogy with Pd^{II} or Pt^{II} is not so close as that statement would imply: There is, of course, no reason why Cu^{II} should form exactly the same number and arrangement of directed bonds as Ni^{II} , Pd^{II} , or Pt^{II} , and careful comparative studies may indicate more subtle differences between the stereochemical behaviour of atoms which form essentially the same number and arrangement of *strongest* bonds. It is supposed that, when Cu^{II} forms four planar bonds (dsp^2), the 35 valency electrons are distributed among the available orbitals as follows:



the odd electron occupying a $4p$ orbital. In the case of Ni^{III} forming four dsp^3 bonds the electronic arrangement is similar except that there is no odd electron. It seems possible that this electron may have some bonding power and might be responsible for two additional weak bonds perpendicular to the plane of the four strong dsp^3 bonds.

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[Received, February 22nd, 1947.]

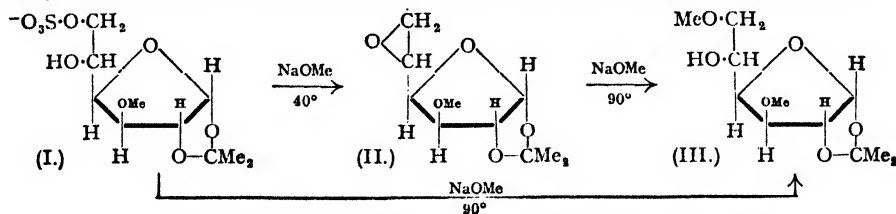
334. Carbohydrate Sulphuric Esters. Part IV. Production of a Derivative of 5:6-Anhydroglucose by the Hydrolysis of a Sulphate.

By R. B. DUFF and E. G. V. PERCIVAL.

By the hydrolysis of barium 3-methyl 1:2-monoacetone glucofuranose 6-sulphate (I), 3-methyl 1:2-monoacetone 5:6-anhydroglucose (II) has been obtained. Unsuccessful attempts to prepare anhydrides from barium 4:6-benzylidene α -methylglucoside sulphate and barium 6-methyl β -methylgalactopyranoside 2-sulphate (VI) are recorded.

IN Part III (J., 1945, 119) it was shown that the hydrolysis with alkali of barium 1:2-monoacetone glucofuranose 6-sulphate yielded 1:2-monoacetone glucofuranose and 1:2-monoacetone 3:6-anhydroglucoside. The failure to identify any *l*-idose derivatives among the products of this hydrolysis was held to prove that no 5:6-anhydride was formed, since Ohle and von Vargha (*Ber.*, 1928, 61, 1203; 1929, 62, 2435) had claimed that, from the corresponding 6-toluene-*p*-sulphonate, 1:2-monoacetone *l*-idofuranose could be obtained *via* the 5:6-anhydride. The basis for this conclusion was destroyed, however, by Seebeck, Meyer, and Reichstein (*Helv. Chim. Acta*, 1944, 27, 1142) who showed that *l*-idose derivatives could not be obtained in this way and that 1:2-monoacetone 5:6-anhydroglucose underwent transformation into the corresponding 3:6-anhydride with great ease. The possibility arose therefore that the 1:2-monoacetone 3:6-anhydroglucose isolated in the experiments from the 6-sulphate (Part III, *loc. cit.*) might have arisen from the 5:6-anhydride as an intermediate.

In order to arrive at an unequivocal decision, a derivative of glucose substituted on C_3 was chosen, to prevent the formation of a 3:6-anhydro-ring. The compound selected, barium 3-methyl 1:2-monoacetone glucofuranose 6-sulphate (I) had the added advantage of solubility in organic solvents which enabled the hydrolysis to be carried out with sodium methoxide instead of aqueous barium hydroxide as in the previous cases (Part III, *loc. cit.*; Part II, J., 1941, 830). Although the method of preparation of (I) does not exclude the possibility that the sulphate group is on C_5 , on general grounds, and by analogy with the reaction with toluene-*p*-sulphonyl chloride (Ohle and von Vargha, *loc. cit.*; Vischer and Reichstein, *Helv. Chim. Acta*, 1944, 27, 1332), this is thought to be highly improbable. Furthermore, it has been shown that by the deacylation of 6-benzoyl 3-benzyl 1:2-monoacetone 5-toluene-*p*-sulphonyl *d*-glucose, 3-benzoyl 1:2-monoacetone 5:6-anhydro-*l*-idose is obtained (Meyer and Reichstein, *Helv. Chim. Acta*, 1946, 29, 152). The possible reaction products in the present case are 3-methyl 1:2-monoacetone glucofuranose by direct hydrolysis and 3-methyl 1:2-monoacetone 5:6-anhydroglucose (II) followed by 3:6-dimethyl 1:2-monoacetone glucofuranose (III) by reaction of (II) with sodium methoxide since the entering methoxyl anion invariably attaches itself to the primary carbon atom (Peat, *Ann. Reports*, 1939, 36, 264).



Experimentally, it was found that although the sulphate group was not removed quite so readily as for the corresponding toluene-*p*-sulphonate, (I) with sodium methoxide (5%) after three hours at 40° gave a transparent barium sulphate gel, and from the reaction mixture 3-methyl 1:2-monoacetone 5:6-anhydroglucose (II, 50%) was obtained, characterised by conversion by sodium methoxide into 3:6-dimethyl 1:2-monoacetone glucofuranose (III)

which on hydrolysis gave crystalline **3** : **6**-dimethyl glucose, identical with an authentic specimen kindly provided by Dr. D. J. Bell, and with specimens prepared by us from **3**-methyl **1** : **2**-monoacetone glucofuranose **6**-toluene-*p*-sulphonate and the corresponding **5** : **6**-ditoluene-*p*-sulphonate.

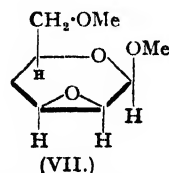
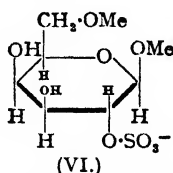
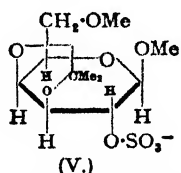
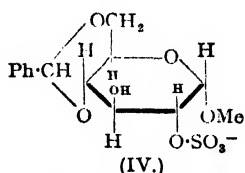
The following table gives the properties of these compounds with the relevant references.

<i>Derivatives prepared from the sulphate (I).</i>	<i>Derivatives prepared from toluene-<i>p</i>-sulphonates.</i>
3 -Methyl monoacetone anhydrohexoside; $n_D^{18} 1.4610$; $[\alpha]_D^{12} -67^\circ$ (<i>c</i> , 4.0 in chloroform)	3 -Methyl 1 : 2 -monoacetone 5 : 6 -anhydroglucose; $n_D^{18} 1.4610$; $[\alpha]_D^{18} -65^\circ \pm 2$ (<i>c</i> , 2.0, in acetone) (Vischer and Reichstein, <i>loc. cit.</i>).
Dimethyl monoacetone hexose; $[\alpha]_D^{18} -46.5^\circ$ (<i>c</i> , 4.5 in chloroform)	3 : 6 -Dimethyl 1 : 2 -monoacetone glucofuranose; $[\alpha]_D^{20} -45.8^\circ$ (<i>c</i> , 4.0 in chloroform) (Bell, <i>J.</i> , 1936, 1553)
Dimethyl hexose; m. p. 115—116°; $[\alpha]_D^{18} +61^\circ$ (<i>c</i> , 0.8 in water at equilibrium)	3 : 6 -Dimethyl glucose; m. p. 114—115°; $[\alpha]_D^{20} +61.6^\circ$ (in water at equilibrium) (Bell, <i>loc. cit.</i>)

There is thus no doubt that ethylene oxide derivatives can be produced from carbohydrate sulphates, and by analogy with the toluene-*p*-sulphonates and methanesulphonates it would be expected that, when the sulphate group is removed from an asymmetric carbon atom with an adjacent *trans*-hydroxyl group, an ethylene oxide ring would be produced with Walden inversion. It is true that the opposite conclusion was reached by one of us (Part III, *loc. cit.*) since the alkaline hydrolysis of barium methylglucoside **3**-sulphate gave only glucose and **3** : **6**-anhydroglucose derivatives, but this could be attributed to the preferential formation of the pentaphan ring.

To test the hypothesis, **4** : **6**-benzylidene α -methylglucoside was treated with chlorosulphonic acid in pyridine to give a barium **4** : **6**-benzylidene α -methylglucoside sulphate. When this was treated in methanol with sodium methoxide, **4** : **6**-benzylidene α -methylglucoside (85%) was recovered and the methoxyl content (10%) of the partly crystalline residue showed that no methoxyl groups had entered the molecule, so that it must be presumed that no ethylene oxide rings had been formed. Whether the product used was a 2-sulphate (IV) or a 3-sulphate, if either had given **2** : **3**-anhydrides, these would certainly have been decomposed by the excess of sodium methoxide with the entry of an additional methoxyl group.

As a further test, **6**-methyl **3** : **4**-monoacetone β -methylgalactoside was synthesised and its structure confirmed by conversion into the known **2** : **6**-dimethyl **3** : **4**-monoacetone β -methylgalactoside (Bell, *J.*, 1945, 692). Barium **6**-methyl **3** : **4**-monoacetone β -methylgalactoside 2-sulphate (V) was then prepared and removal of the isopropylidene residue gave barium **6**-methyl β -methylgalactoside 2-sulphate (VI). When this substance, in methanolic solution, was treated with sodium methoxide, however, no reaction was observed until 90° was reached, whereupon, instead of the production of **6**-methyl **2** : **3**-anhydro- β -methylgalactoside (VII) followed by **2** : **6**-dimethyl β -methylgalactoside or **2** : **6**-dimethyl β -methylidide, or both, rapid darkening of the solution took place with extensive decomposition and the formation of reducing products; no increase in methoxyl content could be detected.



So far, therefore, there is no direct support for the suggestion (*Nature*, 1946, **158**, 29) that sugars may undergo interconversion in *Nature* by way of sulphuric esters and their hydrolysis, even though ethylene oxide formation does occur when the sulphate group on a primary carbon atom is removed. Further work is necessary, however, before this possibility can be abandoned since the behaviour of sulphate residues on C_2 might be anomalous. In connexion with the hydrolysis of (VI) it may be recalled that Helferich and Schnorr (*Annalen*, 1941, **547**, 201) recorded the hydrolysis of a 2-hydroxyethanesulphonic acid glycoside with alkali, and Isbell (*Ann. Rev. Biochem.*, 1943, **12**, 205) has suggested an explanation of this effect in terms of electron displacement initiated by the electronegative sulphonyl group. Until more evidence is available it would be premature to attempt an explanation of the present result, but it is clear that the adjacent sulphate group renders the glycosidic methoxyl labile to alkali. In (VI) it will be noted

that these two groupings are *trans*- to one another which recalls the fact that the alkali fission of the phenylglycosides proceeds most readily when the phenoxy-group is in the *trans*-position with respect to the hydroxyl residue on C₂, as in β -phenylglucoside (Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1848; *J. Org. Chem.*, 1945, **10**, 194; McCloskey and Coleman, *ibid.*, p. 184). If, as is quite likely, the barium 4 : 6-benzylidene α -methylglucoside sulphate is the 2-sulphate (IV), the sulphate and methoxyl groups are in the *cis*-positions, and this might explain why fission of the glycosidic methoxyl was not observed; it is hoped that further work will illuminate these points.

EXPERIMENTAL.

Barium 3-Methyl 1 : 2-Monoacetone Glucofuranose 6-Sulphate.—3-Methyl 1 : 2-monoacetone glucofuranose was prepared as a colourless syrup by the methods of Freudenberg *et al.* (*Ber.*, 1923, **56**, 1225; 1926, **59**, 104). The product had n_D^{20} 1.4740, $[\alpha]_D^{25}$ -54° (c, 3.1, in chloroform) [Found : OMe, 12.8; (CH₃)₂CO, 23.3. Calc. for C₁₀H₁₄O₆ : OMe, 13.2; (CH₃)₂CO, 24.8%].

Sulphation with chlorosulphonic acid (approx. 1 mol.) in pyridine was carried out as described in Part III (*loc. cit.*). In a typical experiment the above syrup (10.1 g.) in dry pyridine (80 c.c.) was vigorously stirred and treated with chlorosulphonic acid (3.65 c.c.) in chloroform (40 c.c.) at -15° . The mixture was neutralised with barium hydroxide solution, the excess being removed with carbon dioxide; it was found necessary to add alcohol to obtain a homogeneous solution, owing to the solubility of the free 1 : 2-monoacetone 3-methyl glucofuranose sulphate in chloroform with the resulting danger of incomplete neutralisation; in some experiments chloroform was removed under reduced pressure at 15° . The crude barium salt (15 g.) was isolated in the usual way and purified by dissolving in twice the minimum volume of acetone followed by partial precipitation (8.1 g.) with light petroleum (b. p. 60–80°); $[\alpha]_D^{25}$ -19° (c, 1.0, in water) [Found : Ba, 18.5; OMe, 8.7; SO₄, 23.2; (CH₃)₂CO, 15.0. (C₁₀H₁₇OS)₂Ba requires Ba, 18.0; OMe, 8.1; SO₄, 25.2; (CH₃)₂CO, 15.2%].

3-Methyl 1 : 2-Monoacetone 5 : 6-Anhydroglucose.—The above barium salt (3.53 g.) was dissolved in warm anhydrous methanol (10 c.c.) and cooled to room temperature. A solution (6.5 c.c.) of sodium (5%) in methanol was added with stirring and the mixture heated at 40° for 3 hours, whereby the mobile liquid was completely converted into a stiff transparent gel owing to separation of colloidal barium sulphate. The gel was treated with excess of a mixture of chloroform and methanol (1 : 1), and carbon dioxide bubbled through until wet phenolphthalein paper was no longer affected. Water (300 c.c.) was then added followed by repeated extraction with chloroform. The combined extracts were dried (Na₂SO₄) and evaporated at 40°/15 mm.; the residual syrup was distilled at 120–130°/0.02 mm. in the presence of barium carbonate (0.2 g.), to give a colourless mobile oil (1.0 g.), $[\alpha]_D^{25}$ -63° (c, 4.5, in chloroform) (Found : OMe, 16.5. Calc. for C₁₀H₁₄O₅ : OMe, 14.4%). Since it was suspected that this product was contaminated with 3 : 6-dimethyl 1 : 2-monoacetone glucose, the crude oil in chloroform (20 c.c.) was adsorbed on a column of aluminium oxide (30 cm. \times 1 cm.). The column was eluted with 5 portions (20 c.c.) of chloroform, and the syrup (0.4 g.) obtained after removing chloroform from the second fraction gave at 120°/0.01 mm. an oil (0.3 g.) which had the properties required for 3-methyl 1 : 2-monoacetone 5 : 6-anhydroglucose; namely n_D^{20} 1.4610, $[\alpha]_D^{25}$ -67° (c, 4.0 in chloroform) (Found : OMe, 14.3. Calc. for C₁₀H₁₄O₅ : OMe, 14.4%).

3 : 6-Dimethyl 1 : 2-Monoacetone Glucofuranose and 3 : 6-Dimethyl Glucose.—3-Methyl 1 : 2-monoacetone 5 : 6-anhydroglucose (0.5 g.) obtained as described above was heated at 90° with a solution of sodium (0.5 g.) in anhydrous methanol (10 c.c.) for 18 hours. Neutralisation by carbon dioxide, dilution with water, and extraction with chloroform was followed by distillation at 110–120°/0.01 mm. to give an oil (0.3 g.), n_D^{20} 1.4622, $[\alpha]_D^{25}$ -46.5° (c, 4.5 in chloroform) (Found : OMe, 21.5. Calc. for C₁₁H₂₀O₅ : OMe, 25.0%).

The above product (0.2 g.) was left at 37° for 48 hours with sulphuric acid (200 c.c.; 0.2N). Neutralisation with barium carbonate followed by filtration and evaporation at 40°/15 mm. gave a sugar which was twice recrystallised from hot ethyl acetate to give crystals (0.1 g.), $[\alpha]_D^{25}$ $+61^\circ$ (c, 0.8 in water; equilibrium value) (Found : C, 46.0; H, 7.5; OMe, 29.8. Calc. for C₈H₁₆O₆ : C, 46.1; H, 7.7; OMe, 30.0%), m. p. 115–116°, unchanged on admixture with an authentic specimen of 3 : 6-dimethyl glucose provided by Dr. D. J. Bell, and with specimens prepared by the action of sodium methoxide on 3-methyl 1 : 2-monoacetone glucofuranose 6-toluene-*p*-sulphonate (Found : OMe, 7.4. Calc. for C₁₇H₂₄O₈S : OMe, 8.0%), and from 3-methyl 1 : 2-monoacetone glucose 5 : 6-ditoluene-*p*-sulphonate (Found : OMe, 5.5. Calc. for C₂₄H₃₀O₁₀S₂ : OMe, 5.7%).

In another experiment the sulphate (2.0 g.) was heated at 90° for 24 hours with sodium in methanol (25 c.c.; 5%). Neutralisation and isolation as previously described gave an oil (0.5 g.), n_D^{20} 1.4637 (Found : OMe, 22.8%) which was treated with sulphuric acid (0.2N) as before, and the sugar purified by filtration through a column of aluminium oxide to give crystals of 3 : 6-dimethyl glucose, m. p. 114°, not depressed on admixture with an authentic specimen.

Barium 4 : 6-Benzylidene α -Methylglucoside Sulphate.—4 : 6-Benzylidene α -methylglucopyranoside, m. p. 163° (10.5 g.), was sulphated as previously described to yield a product (9.5 g.) having $[\alpha]_D^{25}$ $+39.5^\circ$ (c, 1.2 in water) [Found : Ba, 17.6; SO₄, 23.0; OMe, 8.4. (C₁₄H₁₇O₆S)₂Ba requires Ba, 15.9; SO₄, 22.4; OMe, 7.2%]. This was hydrolysed as previously described with excess of a solution of sodium (5%) in methanol at 15° and at 90°. Four such experiments were conducted and in none was any material other than 4 : 6-benzylidene α -methylglucoside obtained from the hydrolysate. In one experiment barium 4 : 6-benzylidene α -methylglucoside sulphate (8.8 g.) was hydrolysed for 18 hours at 90° with sodium methoxide in methanol. The product was dissolved in ethyl acetate and three crops (5.0 g.) of 4 : 6-benzylidene α -methylglucoside were isolated. The residues gave a partly crystalline substance (0.9 g.) which was chiefly 4 : 6-benzylidene α -methylglucoside (Found : OMe, 10.1%).

6-Methyl 3 : 4-Monoacetone β -Methylgalactoside.—6-Methyl β -methylgalactoside (11.0 g.) was

converted into the monoacetone derivative by the method of Ohle and Thiel (*Ber.*, 1933, **66**, 525) as modified by McPhillamy and Elderfield (*J. Org. Chem.*, 1939, **4**, 150). Distillation at 120°/0.01 mm. gave an oil which crystallised at 0°; recrystallisation from ethyl acetate–light petroleum (b. p. 60–80°) gave a product, m. p. 72–74°, $[\alpha]_D^{18} + 11^\circ$ (c, 1.4 in chloroform) [Found: C, 52.8; H, 8.1; OMe, 23.1; $(CH_3)_2CO$, 25.9. $C_{11}H_{18}O_8$ requires C, 53.2; H, 8.1; OMe, 25.0; $(CH_3)_2CO$, 23.4%].

Two methylations (0.4 g.) with Purdie's reagents followed by distillation at 120°/0.01 mm. gave 2:6-dimethyl 3:4-monoacetone β -methylgalactoside (0.35 g.), $[\alpha]_D^{18} + 2^\circ$ (c, 1.0 in chloroform), m. p. 55–56°, unchanged on mixing with an authentic specimen prepared by Dr. D. J. Bell.

Barium 6-Methyl 3:4-Monoacetone β -Methylgalactoside 2-Sulphate.—6-Methyl 3:4-monoacetone β -methylgalactoside (1.7 g.) was sulphated as previously described to yield a barium salt (3.1 g.), $[\alpha]_D^{18} + 10^\circ$ (c, 1.0 in water) [Found: Ba, 18.0; SO_4 , 24.8; $(CH_3)_2CO$, 13.2. $(C_{11}H_{18}O_8)_2Ba$ requires Ba, 17.4; SO_4 , 24.3; $(CH_3)_2CO$, 14.6%].

Barium 6-Methyl β -Methylgalactoside 2-Sulphate.—The above product (2.7 g.) was treated with sulphuric acid (0.2N) at 37° as previously described to yield a non-reducing barium salt (2.3 g.), $[\alpha]_D^{18} \pm 0^\circ$ (c, 1.0 in water) [Found: Ba, 17.5; SO_4 , 25.6; OMe, 15.4. $(C_8H_{15}O_6)_2Ba \cdot 4H_2O$ requires Ba, 17.5; SO_4 , 24.5; OMe, 15.8%]. To this substance (2.0 g.) in methanol (25 c.c.), a solution of sodium in methanol (50 c.c.; 5%) was added. No reaction took place during 24 hours at 15°, 24 hours at 40°, or 6 hours at 60°. When the temperature was raised to 90°, however, the solution rapidly darkened. After 18 hours at 100° the product was worked up in the usual way to give a dark reducing syrup (0.5 g.; OMe, 25.3%). The syrup obtained from a second experiment had OMe, 21.8%. It is thought probable therefore that the syrups obtained were specimens of 6-methyl β -methylgalactoside (OMe, 29.9%) contaminated with reducing material formed by the fission of the glycosidic methoxyl group.

Thanks are expressed to the Carnegie Trust for the Universities of Scotland for a Scholarship (R. B. D.), to Dr. D. J. Bell for the gift of specimens, and to Imperial Chemical Industries Ltd. and the Earl of Moray Endowment for grants.

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[Received, February 20th, 1947.]

335. The Solubility at High Temperatures of Pure Sucrose in Water.

By MILLICENT TAYLOR.

A method of determining the solubility of sucrose at high temperatures has been devised which avoids the necessity of analysis of the solution. In its present form it has been found applicable only to temperatures between 64° and 82°. The relationship between saturation concentration and temperature is expressed by an equation which enables the results to be used in the determination of other thermodynamic properties of sucrose solutions.

THE method to be described was devised with the object of avoiding the filtration at high temperatures and the handling for analytical purposes of highly concentrated, viscous sucrose solutions. The behaviour of a crystal of sucrose in approximately saturated solution of accurately known concentration is observed microscopically during both falling and rising temperature, and the temperatures of incipient healing and erosion are noted. The mean of these two temperatures is taken as the saturation temperature of the solution. The first experiments on these lines were carried out by Dr. A. Wischin, but as she was unable to continue the work, the author undertook preliminary experiments which showed considerable deviation from the results of previous investigators (Herzfeld, *Z. ver. Rübenz.-Ind.*, 1892, 181, 232; Nuszbaum and Grube, *Z. Elektrochem.*, 1928, **34**, 91; Grut, *Z. Zuckerind. Czechoslovak*, 1937, **61**, 356). After some modification of the original apparatus and calibration of all precision instruments, the experiments described below were carried out.

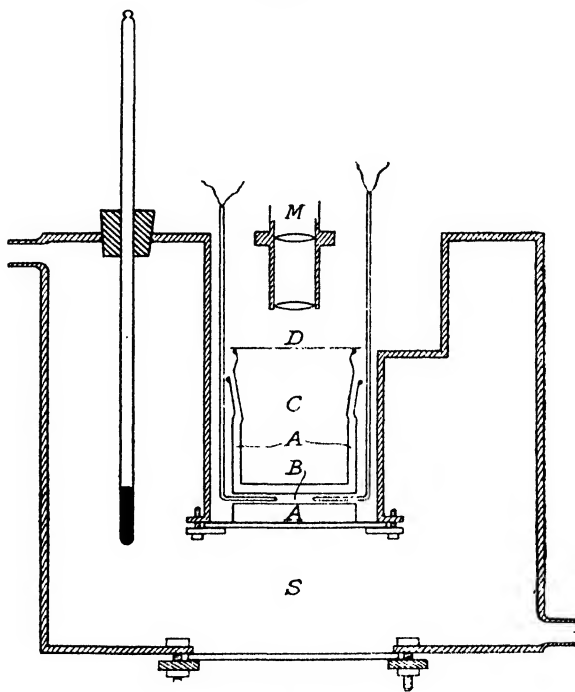
EXPERIMENTAL.

Apparatus.—A glass cell, *A* (Figs. 1 and 2), provided with a horizontal tubular observation shelf, *B*, is closed by a hollow stopper, *C*, the bottom of which is of plane optical glass. The cell slides into a cylindrical water-tight well in the cover of a small lagged thermostat, *S*, the temperature of which is controlled by water pumped from a large thermostat. The lower opening of the well and a corresponding circular opening in the bottom of the thermostat are closed by adaptable plane-glass plates, each held in position by a brass ring and rubber washer. The cell is illuminated through the glass plates by a reflected beam from a 100-watt lamp. A copper–constantan thermocouple consisting of two junctions in series passes into the tubular space under the shelf. The junctions and leads are enclosed for a length of about 8 cm. in very thin drawn-out glass tubing, which is bent at right angles to fit snugly against the side of the cell. A space is left between the junctions to allow of unobstructed microscopic observation of a crystal placed on the shelf between the two junctions. The plate *D*, also of plane optical glass, covering the hollow stopper, is required to prevent irregularities of temperature due to convection currents. Strips of tin foil, in all some 7 or 8 yards in length, are smoothly packed outside the cell and leads, and serve to prevent convection currents in, and to aid conduction of heat across, the annular space surrounding the cell. The latter is also provided with a copper collar carrying a rubber flange which

assists in closing any remaining air space. A mark inside the cell indicates the level at which the solution should stand before insertion of the stopper, which dips considerably under the surface of the solution. A Winkel-Zeiss camera microscope, *M*, which has a visual magnification of about 40 diameters, is used for observation of the crystal.

Calibration.—The thermocouple is calibrated up to 86° on a millivoltmeter reading up to 7 mv., against a standard thermometer (N.P.L.) graduated in 0.1° and correct to 0.02° . For calibration, the thermometer and the thermocouple are immersed to a depth of about 7 cm. in a narrow tube of mercury suspended in a thermostat. The temperature is regulated and read by means of a levelled telescope to about 0.02° . The millivoltmeter is graduated to 0.05 mv. and the reading can be estimated to about 0.005 mv., which corresponds on this instrument, using the two junctions, to approximately 0.05° . The accurate measurement of any temperature difference between the thermocouple under the shelf and the solution on the surface of the latter was initially found to be a matter of some difficulty. The problem was ultimately solved by calibrating the thermocouple *in situ* against the setting or melting points of highly purified samples of palmitic, stearic, and behenic acids, of which the respective setting points are 62.66° , 69.60° , and 80.02° (Professor F. E. Francis, unpublished work). *p*-Chloronitrobenzene, s. p. 83.04° , proves satisfactory at the somewhat higher temperature. The m. p.s were redetermined against

FIG. 1.



Solubility cell in thermostat.

the N.P.L. standard, which was used to calibrate the thermocouple. A sharp m. p. giving reliable results in the second decimal place could not, at first, be obtained. For example, in the case of stearic acid, which gave the least satisfactory value, the recorded m. p. lay between 69.48° and 69.60° . With palmitic acid and behenic acid, the corresponding range was almost negligible. The m. p.s so determined are 62.56° , 69.54° (mean), and 80.00° , respectively.

Two thermocouples, *X* and *Y*, have been used during these experiments. The former was in use during the period when it was impossible to obtain insulating sleeving, and short lengths of drawn-out glass tubing were slid over the leads as a somewhat inconvenient substitute. For the purpose of calibration a small quantity of the ground, purified compound was sealed into a very thin flattened glass tube, which replaced the sucrose crystal on the observation shelf. The cell was then filled up to the mark, in one case with sucrose solution of one of the experimental concentrations, and in another case with water. The change from water to sucrose solution did not affect the readings.

An example of the results obtained by the control calibration of thermocouple *X* is given in Table I.

The use of this mean takes into account the uncertainty in the m. p. of stearic acid and the fact that its m. p. lies between those of the other two acids. Subsequent checking of this calibration showed no significant change in the correction.

When thermocouple *Y* was prepared, insulating sleeving was available and a smoother and more compact tinfoil jacket was applied to the cell. Also, it was found possible to get a sharper comparison of the thermocouple and the standard thermometer by taking as identical in the melting point tube and in the solubility cell the temperature at which crystals shoot out from a partly molten mass, causing the smooth liquid meniscus to become irregular (setting point) or melting back to allow the smooth meniscus

TABLE I.

M. p.s of standards used for calibration of thermocouple X.

Acid.	In m. p. tube.	In solubility cell, read on millivoltmeter.	Correction on thermocouple.
Palmitic	62.56°	62.40°	+0.16°
Stearic	69.54 (mean)	69.45	+0.09
Behenic	80.00	79.84	+0.16
		Mean	+0.16

to re-form (melting point). The difference between the setting and melting points determined in this way lay within the accuracy of calibration of the standard thermometer.

For these reasons, the calibration of thermocouple Y is probably of higher accuracy than that of thermocouple X. The results of the calibration of thermocouple Y are given in Table II.

TABLE II.

M. p.s of standard substances.

Date.	Substance.	In m. p. tube.	In solubility cell, read on millivoltmeter.	Correction on thermocouple.
June, 1945	Palmitic acid	62.62°	62.57°	+0.05°
	Stearic acid	69.54	69.51	+0.03
	<i>p</i> -Chloronitrobenzene	83.04	83.00	+0.04
			Mean	+0.04
Repeated after removal of tinfoil and repacking.				
Sept., 1945	Palmitic acid	62.56	62.57	-0.01
	Stearic acid	69.54	69.55	-0.01
	Behenic acid	79.91	79.94	-0.03
			Mean	-0.02

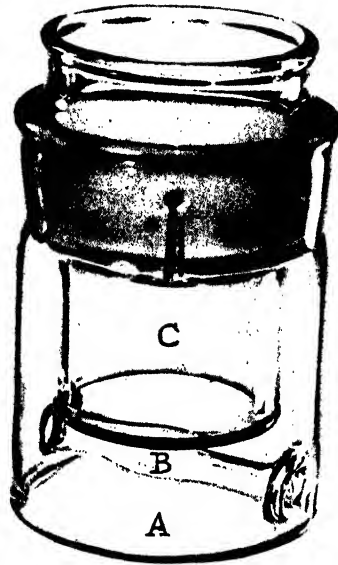
These corrections are within the limits of the error on the thermocouple readings, but they indicate that care must be taken in packing the cell and that frequent recalibration is advisable.

Procedure.—Tate and Lyle's purest sucrose containing on a dry basis 99.99% of sucrose and 0.001—0.003% of invert sugar is very finely ground and dried to constant weight in a vacuum oven under standard conditions (see International Commission for Uniform Methods of Sugar Analysis, London, 1936), *i.e.*, at a temperature not exceeding 60°, in a stream of dried air, the pressure not being allowed to exceed 5 cm. Hg. The air-drying agent used is an activated alumina, having a drying efficiency more than a 1000-fold that of calcium chloride. After being dried, the sucrose is transferred by means of a long, wide thistle funnel to a long-necked, weighed bulb of about 60 c.c. capacity. The lower part of the neck of the bulb has an internal diameter of at least $\frac{1}{8}$ " to allow of unhindered outflow of the viscous solution. The calculated weight of conductivity water for any required concentration is added from a weight burette, provided with a long delivery tube. After thorough mixing at room temperature, the contents of the flask are rapidly frozen in solid carbon dioxide-methylated spirit and after constriction of the neck of the flask the latter is exhausted, the contents are allowed to warm up without admission of air, and the freezing and exhaustion are repeated. The flask is then sealed, subjected to violent automatic shaking for at least an hour at a temperature several degrees higher than the saturation point, and after rapid cooling in ice-water the solution is allowed to reach room temperature for a control weighing.

The seeding crystals, at least two in number and as small as can conveniently be handled, of linear dimensions 0.5—0.25 mm. or less, are placed in position on the shelf of the cell which, with its thermocouple in position, is now connected with the millivoltmeter and is ready to be put into the thermostat. All necessary regulation of the thermostats must be made before the bulb is opened. The cell must, of course, be cold, but the stopper should be slightly warm and greased with a mixture of apiezon grease plus 25% of aluminium stearate. The neck of the bulb, which is clean and dry inside, is then cut across the wide part, and a weighed rubber bung is inserted. After a final control weighing, the result of which has in no case differed by as much as 0.01% from the initial weight of the solution, the latter is cooled to the dew point as determined by a Casella whirling hygrometer, and is quickly poured into the cell. After being closed and before being transferred to the thermostat, the latter is put into a closely fitting, dry beaker and rapidly heated in an electrically controlled water-bath until the temperature indicated by the thermocouple approaches the saturation temperature. The object of this is to check the growth of the seeding crystals and of any centres of crystallisation which are liable to form as the cold solution is poured into the cell. The initial formation of a few such chance crystals may be advantageous as they are very small relatively to the original seeding crystals, are perfectly shaped, and while the smallest disappear rapidly when the saturation temperature is overstepped, a larger one can frequently be retained as a very sensitive temperature indicator. In solutions of higher concentration, 80% and upwards, the deposition of crystals becomes unmanageable, putting an upper limit to the range of concentrations to which this method has been found applicable.

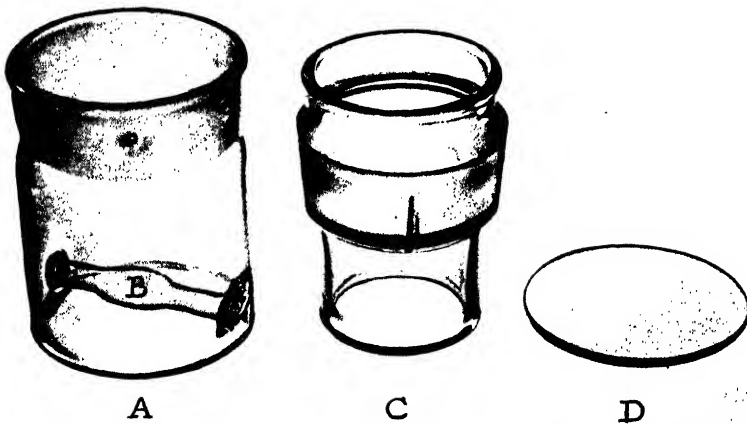
In the thermostat there is considerable time lag in the response of the cell temperature to the thermostat regulation. The lag is probably due to the residual air space in the well of the thermostat and is liable to lead to overstepping of the crucial temperature in either direction. This disadvantage has to some extent been overcome by changing the temperature very slowly. A rate of change of 0.02° per minute has been aimed at, and in most cases it has not been exceeded. A slow rate of change has disadvantages,

FIG. 2a.



Solubility cell. (Actual size.)

FIG. 2b.



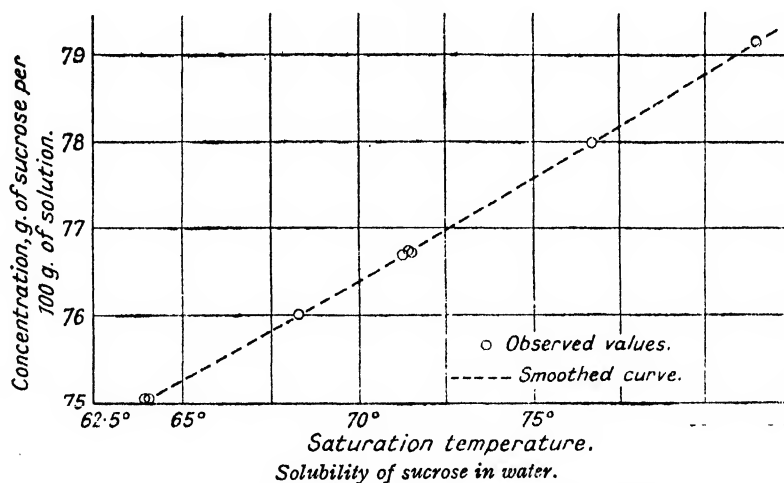
Solubility cell. ($\frac{1}{2}$ Actual size.)

for example, the considerable inversion which is liable to take place, and the possibility of the formation of localities of different concentration either in layers or in the neighbourhood of the crystal. Cautious rocking of the whole thermostat is the limit of disturbance permissible on account of the liability of the crystal to escape from the field of vision, with consequent failure of the experiment. To detect possible errors due to the above-mentioned changes, two pairs of observations of incipient solution and healing temperatures have, when possible, been made with any one solution, and since the results have been found to agree within the limits of the experimental error, the mean of the two pairs of readings is taken as the saturation temperature.

Preliminary experiments were carried out with solutions having saturation temperatures lying between 59° and 62°, but owing to the slow rates of solution and growth at these temperatures, extremely long periods of watching were required, there was a wide interval between the observed incipient erosion and healing temperatures, and the results are somewhat irregular. It was, therefore, decided to limit the experiments to temperatures higher than 64°.

Table III contains a complete record of all the results except those of the above-mentioned tentative experiments and those that gave no reliable result on account of breakdown of the thermocouple or other obvious accident.

FIG. 3.



The solutions are arranged in order of concentration. The letters in the first column give the order in which the solutions were prepared and investigated. The missing letters refer to solutions which gave no result for one or other of the reasons stated above. The numerals in brackets beside the actual temperature readings record the length of time in hours for which the solution had been in the cell when the reading was taken. The final percentage of sucrose inverted, estimated as described later, is recorded in the last column. The remainder of the table is self-explanatory.

TABLE III.

Saturation temperatures of sucrose solutions varying in concentration from 75 to 79 g. of sucrose per 100 g. of solution.

Soln.	Concn., g./100 g. solution.	Thermo- couple.	t_1 , erosion.	t_2 , healing.	Saturation temp., $\frac{t_1 + t_2}{2}$.	Total time in cell (hrs.).	% inverted.
F	75.036	X	64.21° (4)	64.04° (2½)	64.13°	8	0.07
D	75.047	X	64.45 (3)	63.50 (4)	63.98	6	0.22
E	75.050	X	(i) 64.26 (2½)	—	—	—	—
			(ii) 64.26 (5)	64.03 (5½)	64.15	6½	0.18
Q	76.010	Y	68.33 (4½)	68.23 (2)	68.28	5½	0.13
N	76.699	Y	(i) 71.28 (2½)	71.18 (1½)	71.23	—	—
			(ii) 71.28 (3½)	71.18 (4)	71.23	7½	0.20
J	76.730	X	(i) 71.57 (½)	71.46 (1½)	71.52	—	—
			(ii) 71.65 (3)	71.35 (3½)	71.50	3½	0.07
G	76.740	X	(i) 71.50 (1½)	71.32 (1)	71.41	—	—
			(ii) 71.55 (5½)	71.32 (6)	71.44	7	0.31
H	76.747	X	71.58 (2½)	71.22 (3½)	71.40	8	0.10
R	77.994	Y	76.80 (4½)	76.65 (3½)	76.72	7½	0.17
O	79.144	Y	81.44 (5½)	81.40 (2)	81.42	7½	0.50
M	79.172	Y	81.44 (3½)	81.34 (1½)	81.39	7½	1.0

Fig. 3 is a graphic record of the results collected in Table III. The broken line represents the smoothed curve of best fit, calculated by the method of least mean squares, on the assumption that the

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concentrations are correct to the third decimal place. The mean of two determinations of saturation temperature for one and the same solution is given the same weight in the calculation as the single determination in the case of the other solutions.

The equation for the curve is $C = 63.608 + 0.1322t + 0.00722t^2$, where C is the concentration in g. of sucrose per 100 g. of solution and t is the saturation temperature ($^{\circ}\text{C}.$). The calculated probable error of observation is $\pm 0.053^{\circ}$ in the sense that the chances that the error is greater or less than the true value are even. This error is of the same order as the observed uncertainty in the reading of the millivoltmeter.

The readings in Table III, recording saturation temperatures at different times for any one solution, show that any progressive change such as inversion or possible evaporation during the observations has had no appreciable effect on the saturation temperature. Also, different solutions of approximately the same initial concentration give closely concordant values.

TABLE IV.

Saturation concentrations of aqueous solutions of pure sucrose from 64° to 82°, in g. per 100 g. of solution.

Temp.	Herzfeld.	Grut.	Taylor.	Temp.	Herzfeld.	Grut.	Taylor.
64°	74.98	75.41	75.026	74°	77.06	77.71	77.345
65	75.18	75.64	75.251	75	77.27	77.95	77.584
66	75.38	75.86	75.478	76	77.48	78.18	77.825
67	75.59	76.09	75.706	77	77.70	78.42	78.068
68	75.80	76.31	75.936	78	77.92	78.66	78.312
69	76.01	76.54	76.168	79	78.14	78.90	78.558
70	76.22	76.78	76.400	80	78.36	79.15	78.805
71	76.43	77.01	76.634	81	78.58	—	79.053
72	76.64	77.24	76.869	82	78.80	—	79.305
73	76.85	77.47	77.106				

A final control determination of the concentration is impracticable on account of the small size of the cell, the fact that the stopper dips deeply into the viscous solution, and the necessity of removing the stopper before the solution is uniformly cold. Nevertheless, the percentage of sucrose inverted is not affected by evaporation occurring after opening the cell and is determined, after suitable dilution, by refractometer and polarimeter readings. Where inversion is very small the result has been checked by means of de Whalley's colorimetric method (*Intern. Sugar J.*, 1937, **39**, 300; 1944, **46**, 211).

This method has the advantage over methods hitherto described (see below) that the concentration is accurately known and, as the results show, is maintained appreciably constant till the readings are complete. Exposure to the atmosphere occurs only on transfer of the solution to the experimental cell, after accurate cooling to the dew point which, in the absence of crystals, presents no difficulty.

Table IV records saturation concentrations for whole degrees calculated from the equation of the smoothed curve. For purposes of comparison the corresponding saturation concentrations given by Herzfeld and by Grut (*loc. cit.*) are also included. All weights are uncorrected for buoyancy. Herzfeld's equation was $C = 64.1835 + 0.13477t + 0.0005307t^2$ (no probable error given), and calculation shows that his curve would cut ours at 62° . Grut did not suggest an equation.

Discussion.—Herzfeld's equation is undoubtedly distorted by the fact that after a solution had been heated for a long period at 90 — 100° , he determined the saturation concentration of the solution at *ca.* 100° solely by a polarimeter reading. Also, he took no measurements between that temperature and 60° . Experiments in this laboratory have shown that at temperatures exceeding 85° inversion becomes rapid even in a vacuum, and the process is hastened by the presence of air. Consequently, the actual concentration in the above experiments of Herzfeld must have been considerably higher than that indicated by the polarimeter on the assumption that the percentage of invert present was negligible. Grut (*loc. cit.*), on the other hand, gives no satisfactory indication as to how he attacked the problem of loss of water by evaporation. It is, therefore, probable that Herzfeld's saturation concentrations above 60° are too low and Grut's too high. Our values fall between the two. Inspection of Table IV shows that in the concentration region of 78 – 80% , Herzfeld's saturation temperatures are about 2° higher than ours and Grut's about $1\frac{1}{2}^{\circ}$ lower.

There is some confirmation of the validity of our equation in a determination of the solubility of sucrose at 25° by Scatchard, Hamer, and Wood (*J. Amer. Chem. Soc.*, 1938, **60**, 3061), who used an isopiestic method which appears to be extremely accurate as far as temperature measurement is concerned, though the method of drying otherwise pure sucrose is less reliable than the standard method used by us. Nevertheless, the recorded solubility of 67.44 g. of sucrose per 100 g. of solution (corrected for buoyancy) is probably more accurate than any other practically determined value, and it agrees remarkably with the extrapolated value of 67.357% at 25° calculated from our equation, and corrected in this example for buoyancy. If there were error appreciably greater than the calculated probable error in our results, extrapolation should expose it.

In conclusion, it may be pointed out that any method which tends to increase the accuracy of the determination of saturation concentrations is important for the calculation of other thermodynamic relationships. For example, Williamson (*Trans. Faraday Soc.*, 1944, **40**, 435, eqn. 34) has introduced the quantity $(dm/dt)_{\text{sat}}$, where m = mols. of sucrose/1000 g. of water, into an exact equation for the calculation of heats of solution. This quantity is immediately obtained, for any given value of t , from our equation by substitution for C in terms of m and differentiation.

My thanks are due to Mr. Philip Lyle, of Messrs. Tate and Lyle, Ltd., for arranging that this work shall be submitted for publication, to Professor W. E. Garner, C.B.E., F.R.S., for suggesting the method and for helpful advice, and also to Miss Marjorie J. Littleton, B.A., for calculating the equation for the smoothed curve and the probable mean error of the experiment.

This work has been carried out by arrangement with the Ministry of Food, Sugar Division.

THE UNIVERSITY, BRISTOL.

[Received, February 7th, 1947.]

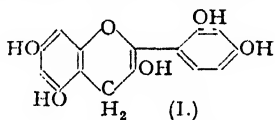
336. *Experiments on the Synthesis of Cyanomaclurin.*

By ERIC L. FONSEKA.

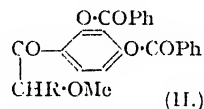
ω -Methoxy-2 : 4-dibenzoylresacetophenone (II, R = H) does not undergo the Mannich reaction, thereby excluding a proposed synthesis of the cyanomaclurin nucleus from (I, R = $\text{CH}_2\cdot\text{NEt}_3$) and phloroglucinol. Catalytic reduction of the flavylum salt (III, R = H) apparently to the flaven (IV, R = H), indicated an alternative route, but the hydrogenation product of O-5 : 2' : 4'-tribenzoyl-O-3-methylmorinidin chloride (III, R = O-COPh), which resembled cyanomaclurin in its colour reactions, could not be recrystallised.

IN the course of experiments on the synthesis of cyanomaclurin (I) (see also Bhalla and Rây, *J.*, 1933, 288; Mitter and Saha, *J. Indian Chem. Soc.*, 1934, **11**, 257; Mitter and Maitra, *ibid.*, 1936, **13**, 236), attempts have been made to prepare a Mannich base, e.g. (II, R = $\text{CH}_2\cdot\text{NEt}_3$), which, on condensation with phloroglucinol, would be expected to give a cyanomaclurin derivative. Despite the use of a wide variety of conditions, ω -methoxy-2 : 4-dibenzoylresacetophenone (II, R = H) failed, however, to undergo the Mannich reaction.

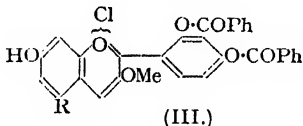
An alternative route was therefore examined, depending on the catalytic reduction of an appropriate flavylum salt. In order to explore the method, experiments were first carried out with 7-hydroxy-2' : 4'-dibenzoyloxy-3-methoxyflavylum chloride (III, R = H), which was



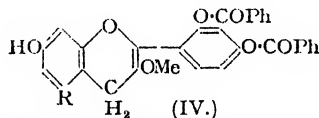
(I.)



(II.)



(III.)



(IV.)

prepared from β -resorcyraldehyde, ω -methoxy-2 : 4-dibenzoylresacetophenone (II, R = H), and hydrogen chloride in ethyl acetate solution. Reduction in acetic acid in presence of Willstätter's platinum catalyst gave a product analysing as a *sesquihydrate* of the flaven (IV, R = H), and showing with alkali and with concentrated sulphuric acid the colour reactions associated with the cyanomaclurin nucleus.

Similarly, the condensation of 2-benzoylphloroglucinaldehyde with (II, R = H) gave the well-defined O-5 : 2' : 4'-tribenzoyl-O-3-methylmorinidin chloride (III, R = O-COPh), which also absorbed two mols. of hydrogen on catalytic reduction. The crude substance likewise exhibited the colour reactions of cyanomaclurin, but all attempts to recrystallise the product for analysis were unsuccessful.

EXPERIMENTAL.

ω -Methoxy-2 : 4-dibenzoylresacetophenone (II, R = H).—Recrystallised ω -methoxyresacetophenone (Slater and Stephen, *J.*, 1920, 312) (13.2 g.) was dissolved in pyridine (65 c.c., redistilled over potassium hydroxide) and the solution cooled in ice while pure benzoyl chloride (24.5 g.) was added with vigorous stirring during 20 minutes. Stirring was continued for $\frac{1}{2}$ hour longer, by which time the smell of benzoyl chloride had practically disappeared, and the mixture left over-night. It was then poured on a mixture

of crushed ice and dilute sulphuric acid, with stirring all the time; a lemon-yellow oil separated, which gradually grew more viscous and finally solidified. The solid was collected, and washed first with cold diluted sulphuric acid and then with water. Recrystallised twice from alcohol, the *dibenzoate* (25 g.) separated in flat needles, m. p. 74–75°, which gave no reaction with ferric chloride (Found, after drying over calcium chloride in a vacuum desiccator: C, 70.8; H, 4.5. $C_{22}H_{18}O_6$ requires C, 70.8; H, 4.6%).

7-Hydroxy-2': 4'-dibenzoyloxy-3-methoxyflavylum Chloride (III, R = H).—Well-dried ω -methoxy-2: 4-dibenzoylresacetophenone (1.18 g.) was dissolved in dry ethyl acetate (30 c.c.). Resorcyaldehyde (0.63 g., dried in a vacuum over sulphuric acid) was added and the mixture warmed to complete solution. The clear liquid was cooled in ice and saturated with dry hydrogen chloride for 2 hours, care being taken to prevent access of moisture. A deep orange-red solution was obtained which was left in a tightly corked flask in the ice chest for 2 days. The *flavylum* salt separated as a red solid which crystallised from hot glacial acetic acid in flat, rectangular, orange prisms (Found, in air-dried substance: C, 62.1; H, 4.4; Cl, 6.2; OMe, 5.4. $C_{30}H_{24}O_7Cl_3 \cdot 3H_2O$ requires C, 61.8; H, 4.6; Cl, 6.1; OMe, 5.3%).

7-Hydroxy-2': 4'-dibenzoyloxy-3-methoxyflaven (IV, R = H).—The *flavylum* salt (1 g.) dissolved in glacial acetic acid (160 c.c.) was placed in a hydrogenation flask with the platinum catalyst (0.1 g.). The absorption of hydrogen, which was fairly rapid up to 35 c.c., slowed down considerably and after 24 hours reached 45 c.c. (2H requires 36 c.c.), while the deep orange-red solution turned light brown. The reduced solution was diluted with a large quantity of ether and the ethereal extract, after being washed with ice water, sodium bicarbonate solution, and then again with ice water, was dried ($CaCl_2$) and the ether removed under reduced pressure at room temperature. A faintly pink solid was obtained which, after repeated precipitations with dry petrol from an ethereal solution, was crystallised from a mixture of these two solvents. The crystals were faintly yellow, and on treatment with sodium hydroxide in the cold gave a blue dichroic solution which turned green on standing. With concentrated sulphuric acid, a claret-red solution was obtained (Found, in substance dried in a vacuum over calcium chloride: C, 69.0; H, 4.6. $C_{30}H_{24}O_7 \cdot 1.5H_2O$ requires C, 69.2; H, 4.7%).

O-5: 2': 4'-tribenzoyl-O-3-methylmorinidin Chloride (III, R = O-COPh).—Pure dry ω -methoxy-2: 4-dibenzoylresacetophenone (5 g.) was dissolved in dry ethyl acetate (100 c.c.), and 2-benzoylphloroglucinaldehyde (3.2 g.) added. The mixture was warmed to ensure complete solution and filtered. The clear solution, cooled in ice, was saturated with dry hydrogen chloride for 3 hours. A small quantity of the sparingly soluble benzoylphloroglucinaldehyde separated and was removed. The clear deep red solution was left in the ice chest for 3 days, but no *flavylum* salt separated. It was then poured into dry ether, and the solid which separated was collected and washed with dry ether. The *salt* was deep red with a green reflex; unlike the resorcinol analogue it was readily soluble in glacial acetic acid. It was crystallised from methyl cyanide, separating in flat orange rectangular plates (Found, in substance dried over sulphuric acid: C, 66.6; H, 3.82; Cl, 5.1. $C_{27}H_{22}O_9Cl_3 \cdot H_2O$ requires C, 66.6; H, 4.05; Cl, 5.3%).

The *flavylum* salt (1 g.) was dissolved in glacial acetic acid (60 c.c.), Willstätter's platinum catalyst (0.1 g.) added, and the solution shaken with hydrogen. The quantity of hydrogen taken up was 34 c.c. (2H requires 34 c.c.). The solution changed in colour from dark orange-red to light brownish-red which darkened considerably in contact with air. It was quickly filtered into ice-water, and the faintly pink solid collected, washed with water, and dried in a vacuum over calcium chloride. In dilute sodium hydroxide solution a faint green colour was observed, which on heating became bright blue, while concentrated sulphuric acid dissolved it to yield a crimson solution.

The author expresses his thanks to Sir Robert Robinson, P.R.S., for advice and encouragement during the course of this work.

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[Received, November 15th, 1946.]

337. The Synthesis of β -6-Methoxyquinolyl(4)ethylamine, β -6-Methoxyquinolyl(4)propionamidine, and β -6-Methoxyquinolyl(4)ethylguanidine.

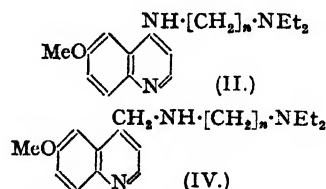
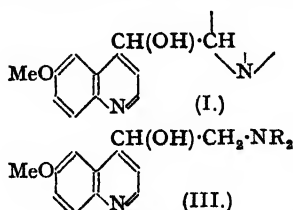
By JAMES WALKER.

β -6-Methoxyquinolyl(4)-ethylamine, -propionamidine, and -ethylguanidine have been synthesized. In common with quinine, each possesses a strongly basic group separated by a chain of two carbon atoms from the 4-position of 6-methoxyquinoline. The substances were devoid of antimalarial activity.

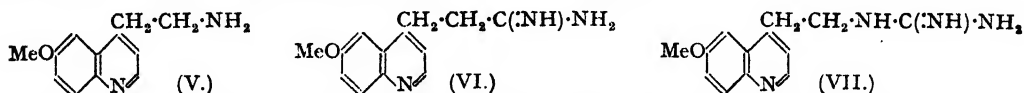
In quinine, the significance of which in the chemotherapy of malaria requires no emphasis, one finds that a strongly basic group is separated from the 4-position of 6-methoxyquinoline by a chain of two carbon atoms as shown in the partial formula (I), where details of the quinuclidine ring system are omitted for the sake of clarity.

Although Giemsa and Oesterlin (*Arch. Schiffs- u. Tropen-Hygiene*, 1933, **37**, Beiheft 4), in studying numerous modifications of the quinine molecule, have attached considerable significance to the alcoholic hydroxyl group, and its replacement in the cinchona alkaloids by chlorine results in loss of antimalarial activity (Cohen and King, *Proc. Roy. Soc.*, 1938, **B**, **125**, 49), the prime necessity for the carbinol group appears to be discounted by the activity of 4- ω -dialkylaminoalkyl-amino-6-methoxyquinolines (II) (Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, **7**, 1896) in

avian malaria. King and his colleagues (*Proc. Roy. Soc.*, 1938, B, 125, 60; *J.*, 1940, 1307) have shown that some latitude is possible with the quinuclidine half of the quinine molecule by demon-



strating antimalarial activity in certain carbinolamines of type (III; R = alkyl), thus inviting comparison of types (II) and (III). Interposing a methylene group between the quinoline ring in (II) and the proximate nitrogen atom of the aliphatic diamine group, giving substances of type (IV), has been shown to have a dystherapeutic effect (Schönhöfer, "Medicine in its Chemical Aspects," 1938, 8, 66; Work, *J.*, 1942, 426). Assuming, in line with current thought regarding the mode of action of drugs, that the antimalarial activity of quinine is due to its interference with the function of an essential structure in the parasite, it is likely that the two basic groups play a large part in the reaction and, if it is due to multipoint fit on a protein, the distance separating the basic centres should be significant. The three bases, β -6-methoxyquinolyl(4)-ethylamine (V), -propionamidine (VI), and -ethylguanidine (VII) were therefore synthesized since, in common with quinine, each possesses a strongly basic group separated by a chain of two carbon atoms from the 4-position of 6-methoxyquinoline.



Condensation of 6-methoxyepidrine with chloral was most advantageously carried out by heating them together at 120° in the presence of a little xylene as a flux. The use of pyridine as solvent at water-bath temperature (Alberts and Bachman, *J. Amer. Chem. Soc.*, 1935, 57, 1284; Clemons and Hoggarth, *J.*, 1939, 1242) was much less satisfactory, the methoxyl group in the 6-position appearing to reduce significantly the reactivity of the methyl group in the other nucleus. Hydrolysis of the resulting $\alpha\alpha\alpha$ -trichloro- β -hydroxy- γ -6-methoxyquinolyl(4)propane (VIII) afforded β -6-methoxyquinolyl(4)acrylic acid (IX), which was also obtained in less satisfactory over-all yield from 6-methoxyquinoline-4-aldehyde and malonic acid. Notwithstanding the use of freshly prepared selenium dioxide (Kaplan, *J. Amer. Chem. Soc.*, 1941, 63, 2654) for the preparation of 6-methoxyquinoline-4-aldehyde, $\alpha\beta$ -bis-6-methoxyquinolyl(4)ethylene (X), together with quininic acid, was formed in considerable amount during the oxidation of 6-methoxyepidrine, indicating the formation of this type of compound not to be attributable solely to ageing of the selenium dioxide used in the oxidation. Hydrogenation of the unsaturated acid (IX) afforded β -6-methoxyquinolyl(4)propionic acid (XI), which was converted through the methyl ester into the hydrazide, from which the amine (V), characterised as the dihydrochloride, was obtained in good yield by Naegeli's modification (*Helv. Chim. Acta*, 1929, 12, 227) of the Curtius degradation. The acid (XI) was also converted through the amide into the nitrile from which the amidine (VI), characterised as the nitrate and as the benzoate, was prepared by the orthodox Pinner method. When 6-methoxyquinolylethylamine (V) was liberated from the dihydrochloride in concentrated aqueous solution with the calculated volume of standard alkali and refluxed with *S*-methylisothiurea sulphate in the usual way, an indifferent yield of the required guanidine (VII) was obtained and the product was difficult to purify. An excellent method, however, was found to be the interaction of the amine (V) dihydrochloride with *S*-methylisothiurea sulphate in concentrated aqueous ammonia at room temperature, the crude guanidine (VII) sulphate readily separating. This seemingly unorthodox technique has previously been used for the conversion of amino-acids into guanidino-acids (D.R.-P. 535,070; Schütte, *Z. physiol. Chem.*, 1943, 279, 52) and is presumably applicable generally to primary and secondary amines which are stronger bases than ammonia, so that the ammonia, present in large excess, competes at a disadvantage with a more powerful nucleophilic reagent for the *S*-methylisothiurea. The guanidine (VII) was characterised as the nitrate.

Tests for therapeutic activity in *P. relictum* infections in canaries were kindly carried out by Dr. Ann Bishop at the Molteno Institute, Cambridge, on (V) (dihydrochloride) and (VI) (nitrate). Miss I. M. Tonkin kindly tested (V) (dihydrochloride), (VI) (nitrate and benzoate), and (VII)

(nitrate) for therapeutic activity in *P. gallinaceum* infections in chicks. No antimalarial action was observed.

EXPERIMENTAL.

6-Methoxylepidine.—The following reduction of 2-chloro-6-methoxylepidine is an improvement on previously described procedures. The chloro-compound (100 g.) (Ainley and King, *Proc. Roy. Soc.*, 1938, B, 125, 60) in alcohol (750 c.c.) containing aqueous sodium hydroxide [23 g. (20% excess) in 75 c.c.] was vigorously stirred (mercury seal) in an atmosphere of hydrogen in the presence of palladised strontium carbonate (9 g.), the vessel being kept in a bath at 50–55° throughout. The anticipated volume of hydrogen was absorbed in a few hours, and the alcohol was removed by distillation from the filtered solution. The crude product was taken up in excess of 2N-sulphuric acid, filtered from any unreduced material, and the reduction product was liberated by careful addition, with stirring, of 40% aqueous sodium hydroxide. The precipitated oil quickly crystallised, affording 6-methoxylepidine monohydrate (88.2 g.; 96%), m. p. 52°.

aaa-Trichloro- β -hydroxy- γ -6-methoxyquinolyl(4)propane (VIII).—6-Methoxylepidine monohydrate (108.7 g.) was dehydrated by exhaustive azeotropic distillation with benzene and then mixed with anhydrous chloral (125 g.; 1½ mols.) and xylene (15 c.c.) which served as a flux. The mixture was heated at 118–120° for 15 hours, becoming solid during the process. The product crystallised from alcohol in colourless rectangular plates (165 g.; 91%), m. p. 196–197° (Found: C, 48.5; H, 4.1; Cl, 33.4. $C_{13}H_{11}O_3NCl_3$ requires C, 48.7; H, 3.7; Cl, 33.2%).

The final mother-liquors were treated in the manner described below with potassium hydroxide to convert any remaining chloral-methoxylepidine into the acrylic acid, but only a small amount (7.5 g.) of unchanged 6-methoxylepidine was recovered.

β -6-Methoxyquinolyl(4)acrylic Acid (IX).—(A) The above chloral-methoxylepidine (146.5 g.) was added in portions to a solution of potassium hydroxide (146 g.) in absolute alcohol (600 c.c.) which was heated and stirred on the water-bath. A vigorous reaction took place after each addition, and finally the mixture was left for one hour on the water-bath. The precipitated potassium chloride was removed and washed with spirit. The alcoholic solution and washings, diluted with an equal volume of water, were concentrated under reduced pressure on the water-bath to remove alcohol. The aqueous solution, treated with norite, afforded, on acidification with glacial acetic acid, a yellow precipitate of the acrylic acid monohydrate (89 g.; 79%). The acid separated from 90% acetic acid in pale yellow fine needles which showed an intense yellow fluorescence in ultra-violet light, m. p. 277–278° (Found: C, 62.9; H, 5.2; loss at 110° in a vacuum, 7.8. Found, for anhydrous material: C, 67.5; H, 4.8. $C_{13}H_{11}O_3N \cdot H_2O$ requires C, 63.2; H, 5.2; H_2O , 7.3. $C_{13}H_{11}O_3N$ requires C, 68.1; H, 4.8%).

(B) 6-Methoxyquinoline-4-aldehyde (29.3 g.) (Kwartler and Lindwall, *J. Amer. Chem. Soc.*, 1937, 59, 524) and malonic acid (37.5 g.) were condensed in pyridine (72 c.c.) containing piperidine (2 c.c.) on the water-bath for 3 hours and finally under reflux for ¼ hour. The product was isolated in the usual way and purified by reprecipitation from solution in excess of aqueous sodium hydroxide and recrystallisation from 90% acetic acid (yield, 25.3 g.; 65%), m. p. 277°.

$\alpha\beta$ -Bis-6-methoxyquinolyl(4)ethylene (X).—The selenium-containing residues from the oxidation of 6-methoxylepidine in dioxan (Kaplan's conditions, *loc. cit.*) were extracted with hot pyridine. The hot solution was treated with norite and cooled, whereupon a solid separated. The solid was extracted with chloroform, and quininic acid remained undissolved, m. p. after recrystallisation from nitrobenzene, 279–280° (Found: C, 65.0; H, 4.2. Calc. for $C_{11}H_9O_3N$: C, 65.0; H, 4.4%). The reddish-orange chloroform extract was filtered through alumina, affording a clear orange solution with a strong greenish-blue fluorescence. Evaporation to dryness and recrystallisation of the residue from ethyl acetate afforded fine yellow prisms of the *ethylene*, m. p. 195–196° [Found: C, 76.6; H, 5.4; N, 8.4; *M* (Rast), 368. $C_{22}H_{19}O_6N_2$ requires C, 77.2; H, 5.3; N, 8.2%; *M*, 342].

β -6-Methoxyquinolyl(4)propionic Acid (XI).—The above acrylic acid (IX) (25.3 g.) was dissolved in a slight excess of 2N-aqueous sodium hydroxide and shaken in an atmosphere of hydrogen in the presence of palladised strontium carbonate (7 g.). The theoretical volume of hydrogen was readily absorbed (in 3 hours) and no further absorption took place on continued shaking (for 1 hour). The product (24.3 g.) was isolated in the usual way. The acid separated from 30% aqueous acetic acid in fine colourless prisms, m. p. 225–226° (Found: C, 67.2; H, 5.6. $C_{13}H_{13}O_3N$ requires C, 67.5; H, 5.6%). The solid and its solution in aqueous acetic acid both showed an intense bluish-white fluorescence in ultra-violet light.

The *methyl ester* (24.9 g.) was obtained by refluxing the acid (25 g.) with methanol (150 c.c.) and concentrated sulphuric acid (9 c.c.) for 8 hours. It was isolated in the normal way, and separated from ligroin containing a little benzene in colourless rectangular prisms, m. p. 90° (Found: C, 68.3; H, 5.9. $C_{14}H_{15}O_3N$ requires C, 68.6; H, 6.1%).

The *amide*, obtained by treating the methyl ester (24.9 g.) in methyl alcohol (50 c.c.) with excess of concentrated aqueous ammonia (300 c.c.) at 37° for 5 days, separated from water in colourless needles (19.6 g.), m. p. 187–188° (Found: C, 67.5; H, 6.0; N, 12.2. $C_{13}H_{14}O_2N_2$ requires C, 67.8; H, 6.1; N, 12.2%).

The *hydrazide*, obtained by refluxing the methyl ester (29.2 g.) with a slight excess of 50% hydrazine hydrate in methyl alcohol (70 c.c.) for 5 hours, separated from spirit in minute colourless prisms (28 g.), m. p. 161–162° (Found: C, 63.2; H, 6.0; N, 16.8. $C_{13}H_{15}O_2N_3$ requires C, 63.7; H, 6.1; N, 17.1%).

β -6-Methoxyquinolyl(4)propionitrile.—The above amide (5.5 g.) was refluxed with phosphorus oxychloride (6 c.c.) in dry chloroform (20 c.c.) for 25 minutes, the solid rapidly dissolving. Solvent and excess of phosphorus oxychloride were removed in a vacuum on the water-bath and the residue was distributed between ether and ice-cold aqueous alkali. The ethereal solution was dried over sodium sulphate and evaporated, the desiccant being washed with acetone to recover some of the product which crystallised out, and the thick colourless syrup (4.9 g.) promptly crystallised on removal of the solvent.

The *nitrile* separated from benzene-ligroin (*ca.* 1 : 1) in clusters of transparent, colourless, rectangular prisms, *m. p.* 96–97° (Found : N, 13.3. $C_{13}H_{12}ON_2$ requires N, 13.2%).

β-6-Methoxyquinolyl(4)propionamidine (VI) *Nitrate*.—A solution of the above nitrile (6.66 g.) in a mixture of absolute alcohol (15 c.c.) and dioxan (15 c.c.) was saturated with hydrogen chloride at 0° and kept in the ice-chest for several days. The solvent and excess of hydrogen chloride were removed at room temperature in a vacuum and the residue was warmed at 37° with 10% alcoholic ammonia (90 c.c.) for a week. The small amount of ammonium chloride was rejected and the filtered solution, on evaporation to dryness, afforded a crude hydrochloride (7.7 g.) which could not be satisfactorily crystallised. The main bulk of the product was dissolved in a small volume of water and treated with a similar solution of an equal weight of ammonium nitrate, and the mixture was evaporated to dryness. The *nitrate* crystallised from about 1½ times its own weight of water in clusters of fine colourless needles, *m. p.* 190–191° (decomp.) (Found : C, 53.3; H, 5.5; N, 18.6. $C_{13}H_{12}ON_3 \cdot HNO_3$ requires C, 53.4; H, 5.5; N, 19.2%).

β-6-Methoxyquinolyl(4)propionamidine *Benzoate*.—The crude amidine hydrochloride, prepared from the nitrile (7.2 g.) as described above, was dissolved in a small volume of water and treated with a slight excess of sodium benzoate in concentrated aqueous solution. The precipitated *benzoate* (11.3 g.) separated from about 8 times its own weight of water in colourless prisms, *m. p.* 192° (Found : C, 68.0; H, 6.0; N, 11.9. $C_{13}H_{12}ON_2 \cdot C_7H_5O_2$ requires C, 68.4; H, 6.0; N, 11.9%). The benzoate was much more soluble in spirit than in water.

β-6-Methoxyquinolyl(4)ethylamine (V) *Dihydrochloride*.—The above hydrazide (31.9 g.) was dissolved in 40% aqueous acetic acid (325 c.c.) and cooled below 0° while an aqueous solution (100 c.c.) of sodium nitrite (36 g.) was added dropwise with thorough stirring. The azide quickly separated and the solid was collected after 1½ hours. The filtrate was neutralised to pH 8.5 with solid sodium carbonate and the azide was re-suspended in the slightly alkaline liquor and again collected, washed with water, and dried overnight in a vacuum over phosphoric oxide. The crude *dry* azide was then cautiously warmed in dry benzene (100 c.c.) until reaction set in. After the spontaneous reaction subsided the mixture was refluxed for 20 minutes and cooled. The brown solution was treated with concentrated hydrochloric acid (50 c.c.) and the benzene was removed on the water-bath after the reaction had ceased. Water was added to keep the hydrochloride in solution, and the *dihydrochloride*, obtained after decolourisation with charcoal and evaporation to dryness, separated from 90% alcohol in fine colourless needles (29.7 g.; 83%), *m. p.* 253° (Found : C, 52.7; H, 6.0; N, 10.4. $C_{13}H_{14}ON_2 \cdot 2HCl$ requires C, 52.4; H, 5.8; N, 10.2%).

β-6-Methoxyquinolyl(4)ethylguanidine (VII) *Nitrate*.—The preceding dihydrochloride (3 g.) and *S*-methylisothiurea sulphate (3 g.; 2 equivs.) were dissolved in concentrated aqueous ammonia (35 c.c.) at room temperature and set aside for 42 hours, crystallisation of solid commencing within 2 hours. The crude methoxyquinolylethylguanidine sulphate was collected, washed with a little water, and dried in a vacuum (yield, 2.8 g.); recrystallisation at this stage afforded a somewhat gelatinous product. The reaction mother-liquors were evaporated to dryness and worked up for nitrate (0.11 g.). The crude sulphate (1 g.) was dissolved in hot water (*ca.* 10 c.c.) and treated with a warm aqueous solution (2 c.c.) of ammonium nitrate (2 g.), whereupon the *nitrate* crystallised out. Recrystallisation from a small volume of water afforded colourless clusters of extremely fine felted needles, *m. p.* 239° (decomp.), giving a positive Sakaguchi reaction (Found : C, 50.6; H, 5.7; N, 22.5. $C_{13}H_{14}ON_4 \cdot HNO_3$ requires C, 50.8; H, 5.6; N, 22.8%). The over-all yield of the nitrate was 70%.

When the foregoing reaction was carried out in hot aqueous solution, using (in the order of mixing) 1 mol. of amine dihydrochloride, 2 mols. of sodium hydroxide, and 1 equiv. of *S*-methylisothiurea sulphate, the yield and quality of the product were markedly inferior.

The author is greatly indebted to Dr. Ann Bishop and to Miss I. M. Tonkin, B.Sc., for kindly carrying out the antimalarial tests, and to Mr. L. V. Sharp for assistance in the preparation of starting materials.

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[Received, February 19th, 1947.]

338. *Hydrated Oxalates of Some Rare-earth Elements.*

By A. W. WYLIE.

The preparation of the "interstitial hydrates" of some cerium-group oxalates and of yttrium oxalate is described. A 6-hydrate and a 2-hydrate of lanthanum oxalate and a 2-hydrate of yttrium oxalate have been prepared. Some properties of these compounds, including optical properties, have been studied, and the structure of the hydrates discussed.

ALTHOUGH numerous hydrates of the rare-earth oxalates have been reported in the literature (Beilstein, "Handbuch der Organischen Chemie", 4th edtn.), confusion persists as to the identity of many of them. Further information about these compounds seems desirable in view of their importance in the chemistry of the rare-earth elements.

It was shown by Löwenstein (*Z. anorg. Chem.*, 1909, 63, 69, 113) that oxalates of lanthanum, cerium, and yttrium containing between 9 and 12 mols. of water per mol. of oxalate varied continuously in composition at a given temperature with the pressure of aqueous vapour. This behaviour is characteristic of a group of hydrates containing what is sometimes termed "zeolitic" water. Although conveniently classing together those hydrates which give a bivalent system

on dehydration, the designation "zeolitic hydrate" is misleading, in that salts such as the rare-earth oxalates of the above-mentioned composition contain none of the interstitial cations present in the natural and synthetic zeolites. Barrer and Ibbitson (*Trans. Faraday Soc.*, 1944, **40**, 195) and Barrer (*Ann. Reports*, 1944, **41**, 31) consider that the state of water and other solutes in the zeolites is best described as an "interstitial solid solution", and since water in the rare-earth oxalates and similar compounds may also be regarded as being in interstitial solid solution, it is proposed to distinguish such compounds as "interstitial hydrates".

The work of Löwenstein and others indicates that substances previously classed as 9-, 10-, and 11-hydrates are to be regarded as interstitial hydrates, to which no definite composition can be attributed, but it is not clear from the literature whether a number of other substances containing considerably more or less water than indicated above are to be included in this category or regarded as separate entities. That the latter alternative is correct is shown subsequently, for the range of composition of interstitial hydrates precipitated from solution and isolated by the usual methods has been found to vary from 9.6 to 10.9 mols. of water per mol. of oxalate.

Well-formed crystals of the interstitial hydrates may readily be obtained by slow precipitation in nitrate solutions at 70°. Chemical and crystallographic evidence shows that these hydrates are identical with an isomorphous series of 11-hydrates described by Wyrnuboff (*Bull. Soc. franç. Min.*, 1901, **24**, 105, 111; 1902, **25**, 66). Identification is most readily made by optical methods owing to variable development of crystal faces and a tendency to adopt different habits according to the mode of preparation.

Conditions for the precipitation of the interstitial hydrates differ from one oxalate to another. For instance, in 3% nitric acid the cerium compound is obtained at temperatures between 0° and 100°. The lanthanum and the yttrium compound, however, are formed only below 80°, 6-hydrates being obtained at higher temperatures. Although lanthanum forms the interstitial hydrate at 0°, yttrium forms a 17- or higher hydrate below 15°. "Didymium" oxalate and the mixed rare-earth oxalates in which cerium predominates resemble the pure cerium compound in behaviour.

The isolation of a 6-hydrate of lanthanum oxalate raises the question of analogous cerium-group oxalates, though no such compounds could be prepared. Since the 6-hydrates of both lanthanum and yttrium oxalate appear to form 2-hydrates on heating, formation of the latter type of hydrate may be general in the case of the 6-hydrates of the yttrium-group oxalates prepared by Marsh (*J.*, 1944, **40**). No 17-hydrate other than $\text{Y}_2(\text{C}_2\text{O}_4)_3 \cdot 17\text{H}_2\text{O}$ (Brauner, *J.*, 1898, **73**, 951; Marsh, *loc. cit.*) has been reported for oxalates of the rare earths, but in view of the behaviour of the so-called 17-hydrate either alone or when mixed with other hydrates, it is possible that a similar or higher hydrate was present in the material described by Wirth (*Z. anorg. Chem.*, 1912, **76**, 174) as a 14-hydrate of erbium oxalate. The degree of hydration of such compounds is unusually high for oxalates.

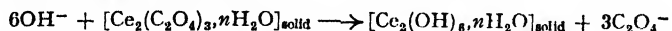
Properties of the Interstitial Hydrates.—Preservation of crystal form and transparency after dehydration is characteristic of this class of hydrate. Density measurements on the cerous compound reveal that dehydration is accompanied by a volume contraction exceeding 27%. The observation that certain inter-edge angles change markedly upon dehydration while other inter-edge angles remain almost unchanged suggests that contraction parallel to the (010) plane exceeds that in other directions. This contention is supported by cleavage of many dehydrated crystals parallel to the (010) plane.

Rapid yet incomplete expulsion of water from these crystals on heating, and resorption of water vapour at lower temperatures by the partly hydrated substances, indicates that transference of water to and from the crystal lattice is readily reversible in the early stages of dehydration. Very slow escape of residual water and similar slow resorption of water vapour by a sufficiently dehydrated product may be attributed to contraction of the interstitial channels. The sorption-desorption mechanism under either of these conditions possibly follows the process of activated diffusion visualised for the natural zeolites by Emmett and De Witt (*J. Amer. Chem. Soc.*, 1943, **65**, 1253) and by Barrer (*Trans. Faraday Soc.*, 1944, **40**, 206, 555). This contrasts with the simpler and more speedy diffusion process operative when the diameter of the channel exceeds the effective diameter of the solute molecules.

The action of water on the partly dehydrated oxalates varies with the extent of dehydration. If this is sufficient to cause extensive changes in the lattice *viz.*, greater than about 90% in the cerium-group oxalates and greater than about 70% in yttrium oxalate, less energy is required to move ions from the lattice to the solution than is involved in transferring a water molecule from solution to an appropriate position in the crystal; solution effects therefore predominate

over sorption effects. An immediate consequence of the entry of ions into solution is the deposition of the fully hydrated interstitial hydrate, which is the appropriate solid phase at the temperature of the system. If the extent of dehydration and lattice rearrangement is less, lattice forces are sufficiently strong to prevent escape of ions and sorption of water by the lattice predominates.

Conversion of rare-earth oxalates into "hydroxides" is usually accomplished by boiling with sodium hydroxide. It has been found that reaction with the interstitial hydrate proceeds rapidly in cold 15% sodium hydroxide. With suitable crystals migration of the phase boundary between newly-formed "hydroxide" and residual crystalline hydrate can readily be followed under the microscope. Initially the process is assumed to involve transfer of hydroxyl and oxalate ions across the ingoing surface:



Since the product appears to be non-crystalline when examined in visible light, possessing only a "relic" structure, it is further assumed that subsequent rearrangement of cerous and hydroxyl ions and of interstitial water molecules occurs, leading to formation of a hydrous oxide or hydroxide of cerium in a gelatinous or microcrystalline condition.

By ignition of the interstitial hydrates in air at 900°, particles of oxides are formed which still retain the sharp outlines of the original hydrate crystals (cf. Urie and Wylie, *J. Soc. Chem. Ind.*, in the press). The channels in the dehydrated oxalate crystal must therefore be sufficiently wide to allow decomposition products of the oxalate radical to escape without disintegration of the structure. Furthermore, the mobility of the anions and cations of the residual oxide must be small at 900°, though sufficient at 1200° to bring about collapse of the relic structure and relatively speedy formation of a thermally stable form of oxide.

Limiting Composition and Structure of Interstitial Hydrates.—The highest values found in this investigation for the molar ratio of water in the lanthanum and cerium hydrates approach 11, a value found by James and Robinson (*J. Amer. Chem. Soc.*, 1913, **35**, 754) for pure neodymium oxalate at 25° in water and solutions of neodymium nitrate. For yttrium oxalate this molar ratio approaches 10 in samples known to be homogeneous. No study of the composition of this solid in contact with water or aqueous solutions has been reported. If the interstitial hydrates were strictly isomorphous, the number of interstitial positions available to water molecules should be the same in each hydrate and the maximum molar ratio should be 11 for oxalates of both the cerium and the yttrium group. Yttrium oxalate, however, differs in a number of respects from the cerium-group oxalates and strict isomorphism cannot be assumed. These differences must ultimately be traced to differences in the ionic radii and polarisabilities of the cations.

Since James and Robinson found that the "11-hydrate" of neodymium oxalate behaved as a definite compound it must be assumed, in order to reconcile this result with the properties of the solid interstitial hydrates, that the substance $\text{M}_2(\text{C}_2\text{O}_4)_3 \cdot 11\text{H}_2\text{O}$ (where M is a rare-earth element) forms a continuous series of solid solutions with its dehydration products. This interpretation requires that the *p-c* isotherms of the system oxalate-water vapour should extrapolate to the same composition for the interstitial hydrates of lanthanum, cerium, and neodymium. As the curves obtained by Löwenstein (*loc. cit.*) show little indication of behaving in this fashion at 25°, it is assumed that the systems investigated were not in equilibrium. It seems doubtful if the curve given for erbium oxalate was obtained with homogeneous material.

No X-ray determination of the crystal structures of rare-earth oxalates has been made. It is assumed that water molecules are held in the lattice of the interstitial hydrates in interstices between the cations and the larger oxalate ions, the latter of which have a predominating effect in determining the crystal structure. Forces restraining water molecules in the lattice presumably consist of electrostatic forces (ion-dipole and ion-induced dipole forces) and dispersion forces. In the fully saturated hydrates $\text{M}_2(\text{C}_2\text{O}_4)_3 \cdot 11\text{H}_2\text{O}$ in which all available interstitial positions are occupied by water molecules an ordered arrangement of solute molecules may be assumed, whereas in the partly hydrated substances the distribution of water molecules is assumed to be statistical.

A survey of the optical properties of various forms of oxalic acid and its salts reveals that the great majority of these substances resemble the rare-earth oxalates in forming strongly birefringent monoclinic crystals. This behaviour may largely be attributed to the high refracting power and anisotropy of the oxalate ion (Evans, "Crystal Chemistry", Cambridge Univ. Press, 1939, **24**, 270; Wooster, *Z. Krist.*, 1931, **80**, 495; Robertson, *J.*, 1936, 1817). The optical data appear to exclude the possibility of a layer lattice in the interstitial hydrates. The

almost isotropic character of the crystals formed by expulsion of water from the lanthanum and cerium hydrates may be explained by assuming rotation of planar oxalate ions about a centre until, when 90% or more of the water is expelled, the anions of the lattice consist of oxalate groups inclined in all directions in space. A similar arrangement is not reached in yttrium oxalate owing to decomposition of the oxalate before sufficient water can be expelled to allow the necessary degree of rotation of the anions.

EXPERIMENTAL.

Purity of Materials.—Commercial brands of lanthanum, cerium, and yttrium nitrates "free from other rare earths" were employed as the hexahydrates. *Lanthanum nitrate.* The only impurities detected were phosphate (0.01%) and traces of calcium; the average atomic weight, calculated from the ratio $\text{La}_2\text{O}_3 : 3\text{C}_2\text{O}_4$, was 138.6. *Cerous nitrate.* Traces of phosphate were present; the average atomic weight, calculated from the ratio $2\text{CeCO}_3 : 3\text{C}_2\text{O}_4$, was 140.3. *"Didymium" nitrate.* A salt containing a preponderating amount of neodymium nitrate was used. *Yttrium nitrate.* A 10-cm. thickness of a 2M-solution showed faint absorption lines due to erbium and holmium; the average atomic weight was 89.4 and this value was used in calculating the composition of various hydrates of yttrium oxalate. *Mixed cerium-group nitrates.* These, containing thorium, were prepared from the mixed hydroxides by dissolving them in nitric acid and reducing ceric nitrate by addition of hydrogen peroxide.

Solutions for precipitation were placed in a thermostat, and 10% oxalic acid added in excess unless stated otherwise. The rate of precipitation was varied by controlling the rate of addition of oxalic acid. Products formed at 50° or above were digested in solution for 1 hour before being filtered; below 50° the digestion time was 4 hours. Each hydrate was washed four times with water at the temperature of precipitation, and after treatment with alcohol and ether was dried to constant weight in air and transferred to sealed jars.

All samples were examined under the microscope for homogeneity before analysis.

The oxalate radical was determined by dissolving the compound in warm 10% sulphuric acid and titrating at 80° with 0.1N-potassium permanganate. Oxides were determined by igniting the oxalates to 1000°. Cerium, determined volumetrically by oxidation with ammonium persulphate followed by titration with ferrous ammonium sulphate (tri-*o*-phenanthrolineferrous complex indicator), agreed satisfactorily with results obtained by the ignition method. The oxalate was first brought into solution by heating with ammonium persulphate, sulphuric acid, and silver nitrate (Axt, *J. Soc. Chem. Ind.*, 1941, 60, 229).

Lanthanum Oxalate.—The solutions contained (a) lanthanum nitrate 10 g., 66% nitric acid 3 ml., water 100 ml., and (b) lanthanum nitrate 5 g., 66% nitric acid 3 ml., water 1 l.

Solu- tion.	Temp.	Precipitation time, mins.	Molar ratio of water in product.	Remarks.
a	98—75°	120	6.00 *	Small granular crystals and aggregates
b	50	3	7.5—8.6	Mixture
		60	10.5	Interstitial hydrate,† well-formed crystals
		5	10.5	" " poorly-formed crystals
	20	60	10.4, 10.4	" " globular aggregates
	0	60	10.4, 10.6	" " " "

* Found: La_2O_3 , 50.1, 50.0; C_2O_4 , 40.6, 40.6. $\text{La}_3(\text{C}_2\text{O}_4)_3 \cdot 6\text{H}_2\text{O}$ requires La_2O_3 , 50.1; C_2O_4 , 40.6%.

† Also formed by adding just insufficient oxalic acid to cause precipitation at 75°, and cooling to 20°.

At 180° the hexahydrate appears to form a stable dihydrate [Loss of wt., 11.1—11.3. Required for loss of $4\text{H}_2\text{O}$, 11.1%. Found: C_2O_4 , 45.7. $\text{La}_3(\text{C}_2\text{O}_4)_3 \cdot 2\text{H}_2\text{O}$ requires C_2O_4 , 45.7%].

The interstitial hydrate at 180° rapidly lost up to 85% of its water content. A further 10% was lost very slowly, even in a vacuum, the molar ratio of water in the residue falling to approximately 0.53 after 142 hours without constancy in composition being reached. At 280° the oxalate slowly decomposed. When dehydration was somewhat less than 85% complete, the residues resorbed water when placed in an atmosphere of water vapour at 20°, at first rapidly and then more slowly, resorption being eventually complete. When dehydration was more than 85% complete, reaction with water vapour was very slow, less than 7% of the total water content being resorbed after 100 hours.

When heated with 5.7N-sulphuric acid for 2 days at 25°, the interstitial hydrate formed rectangular, lath-shaped crystals belonging to the orthorhombic or tetragonal system. Although sulphate could not be completely removed by washing with water without decomposing the crystals, the composition approximated to the 7-hydrate described by Brauner and Pavlicek (*J.*, 1902, 81, 1264) and by Wirth (*Z. anorg. Chem.*, 1908, 58, 226).

Cerous Oxalate.—Solutions (a) and (b) were similar in composition to those used for preparation of lanthanum oxalate.

Solu- tion.	Temp.	Precipitation time, hrs.	Molar ratio of water in product.	Remarks.
a	101°	3.5	8.5—9.2	Mixture of interstitial hydrate and lesser amount of small granular crystals
b	98	1	10.3	Interstitial hydrate, well-formed crystals
		2	10.6	" " " "
a	80	1	10.3—10.6	" " " "
	20	1	10.8, 10.9	" " globular aggregates
	0	2	10.9	" " " "

Attempts to prepare a pure 6-hydrate by boiling the interstitial hydrate for 17 hours in water or 1% nitric acid were unsuccessful.

The rates of dehydration of the interstitial hydrate at 180° and of resorption of water vapour at 20° were very similar to the rates observed for the analogous lanthanum hydrate. Prolonged heating in air caused slow formation of a yellow ceric compound, although approximately 92% of the water content could be removed in a vacuum at 180° without decomposition of the oxalate. Rapid oxidation in air occurred at 280°.

The contraction of the interstitial hydrate during dehydration was followed by determining the density of well-formed crystals in bromobenzene at 25° ± 0.01°. This substance is known to be occluded to a negligible extent by dehydrated zeolites (Barrer, *Ann. Reports*, 1944, 41, 44):

Molar ratio of water	10.5	8.36	5.00	2.81	1.18
d_{25}^{25}	2.36, 2.36 *	2.47	2.72	3.02	3.27

* Determined in kerosene.

The density of the final product was equivalent to a contraction in volume of 27.9%.

Yttrium Oxalate.—The solution contained yttrium nitrate 3 g., 66% nitric acid 2 ml., water 100 ml. Duration of precipitation was 2 hours.

Temp.	Molar ratio of water in product.	Remarks.
98°	6.00 *	Short, thick, well-formed crystals
80	7.5—8.5	Mixture
70	9.62, 9.92	Interstitial hydrate, well-formed crystals
25	10.4, 12.9	Mixture of aggregate and poorly-formed crystals
15	16.8, 10.1	Globular aggregates of very small crystals
9	14.8	" " " " "
0	15.5, 16.7, 15.8 †	" " " " "

* Found: Y_2O_3 , 41.1, 41.2; C_2O_4 , 47.9, 48.0. Calc., for $Y_2(C_2O_4)_3 \cdot 6H_2O$; Y_2O_3 , 41.2; C_2O_4 , 47.9%.

† Precipitate digested in mother-liquor for 72 hours.

Precipitates formed at 25° or below appeared to consist either of mixtures of the interstitial hydrate and a higher hydrate such as the 17-hydrate described by Brauner (*loc. cit.*) and by Marsh (*loc. cit.*) or else of a second interstitial hydrate containing approximately 17 or more mols. of water per mol. of oxalate. Physicochemical data are required to reveal the true nature of the solid phase.

Both the interstitial hydrate and the unidentified hydrate obtained below 25° gave the 6-hydrate when heated in water for 7 hours at 98°.

A dihydrate was formed from the hexahydrate at 180° [Found: C_2O_4 , 55.0, 55.0. $Y_2(C_2O_4)_3 \cdot 2H_2O$ requires C_2O_4 , 55.1%. Loss of wt., 13.1. Required for $4H_2O$, 13.1%].

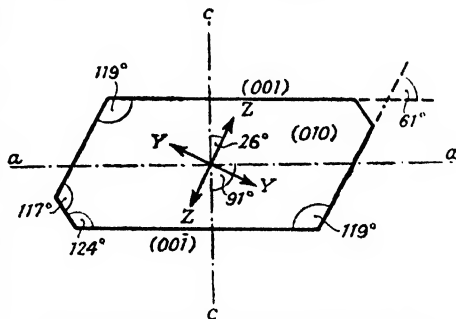
At 180° the interstitial hydrate readily lost approximately 57% of its water content. A further 20% was lost more slowly, leaving a residue in which the molar ratio of water was 2.1—2.2. The unidentified hydrate gave a similar residue at 180°. No further loss of water took place at 220°, and at 280° the oxalate slowly decomposed. Resorption of water vapour at 20° was comparatively rapid when dehydration of the interstitial hydrate was less than 57% complete; beyond this point water vapour was taken up much more slowly, less than 15% of the total water content being resorbed after 45 hours.

"Didymium" Oxalate.—Between 50° and 98° only the interstitial hydrate was precipitated from didymium nitrate solutions comparable in composition to solution (b) used for the preparation of lanthanum oxalate.

Mixed Oxalates.—Solution (a) contained mixed nitrates 10 g., 66% nitric acid 38 ml., water 1 l. Solution (b) contained rare-earth oxides 5.1 g., thoria 0.6 g., sulphuric acid 18.0 g., phosphoric acid 3.2 g., water 100 ml., and was obtained by heating monazite with sulphuric acid, dissolving the sulphates in water and filtering the solution. The interstitial hydrate was the only hydrate obtained from either solution (a) (50—98°) or (b) (80—98°). Crystals precipitated in (a) differed in habit from those precipitated in (b), the former resembling crystals precipitated from lanthanum or cerous nitrate solution. The identity of these products was established by determining the optical properties of the crystals.

Microscopical Examination of Interstitial Hydrate and Reaction Products.—Crystals 40—400 μ in length, surfaces often curved. Inclusions numerous if rapidly precipitated. Flattened perpendicular to *b* axis if deposited by cooling saturated acid solutions.

For lanthanum, cerium, and yttrium hydrates with molar ratios of water 10.3, 10.4, and 9.92, respectively, optical properties were: crystals monoclinic, optically—, $X = b$, $Z \wedge c = 26^\circ \pm 2^\circ$, $2V$ large. Elongation, — in nitrate solution, + in sulphuric-phosphoric acid solution. Refractive indices: α 1.47(5), β 1.55, γ 1.61 [except for the yttrium hydrate: α 1.48(5), β 1.55, γ 1.61]. No changes in α , β , or γ were detected for variations of $\pm 2\%$ in the above values of the molar ratio of water. Cleavage was distinct parallel to (010). The (001) face often showed striae parallel to the 010 edge. "Didymium" and the mixed rare-earth compounds were almost optically identical with the lanthanum and cerium compounds.



Optical orientation of interstitial hydrates.

None of these observations conflicts with a meagre description of a series of 11-hydrates of cerium-group oxalates given by Wyrouboff (*loc. cit.*) with the exception of the angle $Z \wedge c$, which was said to be 18° . The figure gives the optical orientation of the interstitial hydrates, $c \wedge a$ being the axial angle given in Wyrouboff's paper for the lanthanum compound.

Transparent crystals preserving the outline of the parent substance were obtained when 90% of the water of hydration was removed (180°) from lanthanum or cerous oxalate. Although no change was detected in profile views of the (010) face (see fig.), yet profile views of the (001) face disclosed marked changes in inter-edge angles. Cleavage of a number of crystals along the 010 plane was noted. The dehydrated crystals were weakly birefringent and the average refractive index was 1.68—1.69. When treated with water at 20° , these crystals were gradually changed into a mass of small (2—10 μ) acicular crystals, the optical properties of which, as far as could be determined, resembled those of the fully hydrated interstitial hydrate. The recrystallisation process was slightly exothermic. The optical properties of the partly (40—70%) dehydrated oxalates were of an intermediate character, smaller or thinner crystals being apparently dehydrated to a greater extent than others in the same sample. The former reacted with water only if the extent of dehydration approached 90%.

Transparent crystals resembling the parent substance were obtained at 180° only from thin crystals of yttrium oxalate, thicker specimens disintegrating on heating. After loss of 75% of the total water content, a brittle residue was obtained with approximate refractive indices: α 1.50, β 1.67, γ 1.67—1.68. Treatment with water changed this residue into small rectangular laths of the interstitial hydrate.

After ignition for 1 hour at 900° , the interstitial hydrates formed coherent particles of oxides closely resembling the parent crystals, providing these were thin. The particles were highly refractive and the majority showed aggregate polarisation. Prolonged ignition completely destroyed the outline of the original crystals and resulted in formation of opaque, sintered products.

By boiling with 15% aqueous sodium hydroxide the interstitial hydrates were converted into "hydroxides" consisting of discrete particles similar in shape to the parent substance. The particles were isotropic or faintly birefringent. By observing the process on a microscope slide the rate of attack was seen to be rapid even at 20° . The sodium oxalate produced separated from solution in radiating clusters of acicular crystals.

Microscopical Examination of Hexahydrate of Yttrium Oxalate.—Crystals monoclinic, 20—60 μ in length, often pinacoidal parallel to c axis and flattened parallel to (100). Cleavage distinct parallel to (010). Optically—, $X = b$, $Z \wedge c = 40^\circ$, $2V$ small, α 1.47, β 1.61, γ 1.62. A granular mass of small birefringent fragments was formed on heating to 180° . The crystals swelled and disintegrated when treated with 15% sodium hydroxide.

Crystals of the hexahydrate of lanthanum oxalate were too small for satisfactory optical examination.

The author wishes to acknowledge the assistance of Dr. A. R. Alderman and Mr. A. J. Gaskin with the optical determinations.

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[Received, February 6th, 1947.]

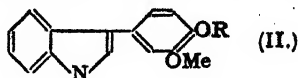
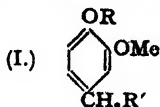
339. Homovanillin.

By A. A. L. CHALLIS and G. R. CLEMO.

Homovanillin (I; $R = H$, $R' = CHO$) was prepared in 65% yield by ozonolysis of *O*-carbethoxyeugenol, followed by catalytic decomposition of the ozonide, and removal of the hydroxyl-protecting group by mild hydrolysis. Eugenol methyl ether and acetyl- and carbobenzyloxy-eugenol similarly gave the analogously substituted homovanillins.

Homovanillin and its derivatives were used in the Fischer indole synthesis, and the Strecker amino-acid synthesis; and condensation with cyclohexanone followed by cyclisation and dehydrogenation provided a new route to substituted phenanthrenes.

HOMOVANILLIN was obtained in poor yield by Harries and Haarmann (*Ber.*, 1915, 48, 29, 868) by ozonolysis of eugenol and decomposition of the ozonide by zinc and acetic acid. We have found that at 0° and in ordinary freezing mixtures a solution of *O*-carbethoxyeugenol (I; $R = CO_2Et$, $R' = \cdot CH_2CH_3$) in ethyl acetate with excess of ozone gives chiefly *O*-carbethoxyhomovanillic acid, but at -70° 5% ozone is almost completely utilised if the special vessel illustrated in the figure is employed, and if the ozonide is immediately decomposed by shaking with hydrogen and palladised charcoal (cf. Henne and Perilstein, *J. Amer. Chem. Soc.*, 1943, 65, 2183), good yields of *O*-carbethoxyhomovanillin were produced which could be converted into homovanillin by hydrolysis in dry 2% alcoholic hydrochloric acid. The final product—a viscous pale yellow oil—did not solidify, but gave a *p*-nitrophenylhydrazone, a 2:4-dinitrophenylhydrazone, and a semicarbazone, all in 85—90% yield. In the presence of even small amounts of aqueous alkali or acid, the homovanillin polymerised, but otherwise was quite stable.



O-Acetylhomovanillin was prepared in an analogous manner. Oxidation in very dilute potassium permanganate solution containing excess of magnesium sulphate gave *O*-acetylhomovanillic acid; more vigorous conditions gave *O*-acetylvanillic acid. Nitration of *O*-acetylhomovanillin in acetic anhydride with the theoretical quantity of nitric acid for either the mono- or the dinitro-compound gave nitrogenous red oils which would not solidify and could not be distilled.

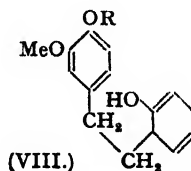
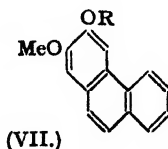
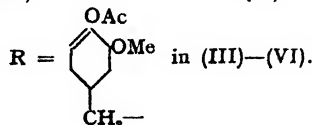
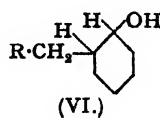
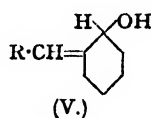
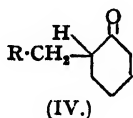
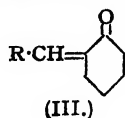
It was found that the ozonide of *O*-carbobenzyloxyeugenol (I; $R = CO_2CH_2Ph$, $R' = CH_2CH_3$) (Bergmann and Zervas, *Ber.*, 1932, 65, 1194; Olcott, *J. Amer. Chem. Soc.*, 1939, 59, 392) gave only *O*-carbobenzyloxyhomovanillin (I; $R = CO_2CH_2Ph$, $R' = CHO$) on catalytic reduction. The use of large amounts of catalyst did not result in hydrogenolysis to homovanillin.

Homovanillin phenylhydrazone was used in a Fischer indole synthesis giving 3-4'-hydroxy-3'-methoxyphenylindole (II; $R = H$). This gave only a slight colour in the Ehrlich rosindole reaction (indoles substituted in position 3 usually give this reaction, and the failure in this case may be due to steric hindrance of the substituent, since neither 2- nor 3-phenylindole gives a colour), but the pine-shaving test was strong, ferric chloride gave a deep red colour, and concentrated sulphuric acid a series of colour changes.

The hydroxyl group of the indole was readily acetylated and benzoylated. These derivatives gave only slight colours in the rosindole test. With the pine-shaving a good violet colour was obtained, but no colour was given with ferric chloride.

O-Acetylhomovanillin was used in a Strecker synthesis of β -4-hydroxy-3-methoxyphenylalanine [I; $R = H$, $R' = CH(NH_2)CO_2H$]. A slight modification of the general method of Cocker and Lapworth (*J.*, 1931, 1391) was used, but the yield obtained (ca. 30%) does not compare with the 65% by the synthesis of Johnson and Bengis (*J. Amer. Chem. Soc.*, 1913, 35, 1613), who hydrolysed vanillylhydantoin, obtained by the reduction of vanillylidenehydantoin, with barium hydroxide.

O-Acetylhomovanillin was condensed with cyclohexanone in technical pyridine to give the homovanillylidene derivative (III), which crystallised only with difficulty, possibly owing to the presence of geometrical isomers; the dihydro-compound (IV) crystallised fairly readily. This was obtained by reduction of (III) either with sodium amalgam in alcohol-acetic acid, or by catalytic hydrogenation, using Adams's catalyst; it was saturated but still gave an oxime. On prolonged refluxing of a moist ethereal solution of (III) with aluminium amalgam, a compound was obtained which was unsaturated and non-ketonic and was consequently formulated as (V). This compound also was difficult to obtain crystalline and when catalytically hydrogenated gave a non-ketonic saturated dihydro-compound identical with that obtained by action of aluminium amalgam on (IV). The latter gives a benzoyl derivative; and is therefore 2-*O*-acetylhomovanillyl-cyclohexanol (VI).



Attempts to cyclise it by using sodium ethoxide, syrupy phosphoric acid, or phosphoric oxide in benzene all failed. This may be due to the fact that while free rotation about the carbon bonds of the atoms joining the two cyclic systems allows favourable orientation of the hydrogen and hydroxyl groups on the two rings, all three bonds would have to be in definite positions to enable this orientation to take place. The substance (III), however, was found to cyclise in small yield in either a boiling benzene suspension of phosphoric oxide or on standing at room temperature in a chloroform solution of phosphorus oxychloride. With these drastic

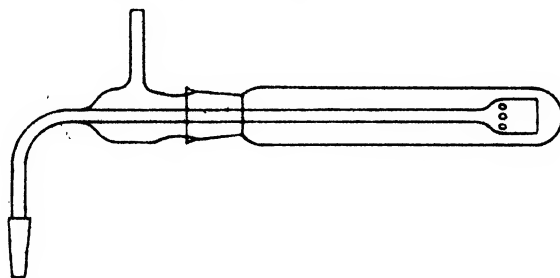
reagents, enolisation and isomerisation of (III) to (VIII) would be expected; this would then cyclise *para* to the methoxy-group and aromatisation would occur to give 3-acetoxy-2-methoxy-9:10-dihydrophenanthrene. This structure was confirmed by a fairly smooth selenium dehydrogenation of the cyclisation product to phenanthrene. Further, less drastic dehydrogenation by heating to 210–220° with palladium-black (Majima and Murahs, *Proc. Imp. Acad. Japan*, 1934, 10, 342) gave 3-acetoxy-2-methoxyphenanthrene (VII, R = Ac; Gilman and Cook, *J. Amer. Chem. Soc.*, 1940, 62, 2816), which was hydrolysed to 3-hydroxy-2-methoxyphenanthrene (VII, R = H; Gilman and Cook, *loc. cit.*); methylation gave 2:3-dimethoxyphenanthrene (VII, R = Me; Pschorr and Buckow, *Ber.*, 1900, 33, 1831).

EXPERIMENTAL.

(All m. p.s and b. p.s are uncorrected. Sodium sulphate was used as the drying agent unless otherwise stated.)

O-Carboethoxyeugenol.—Sodium hydroxide solution (35 g., 40%) was added dropwise with cooling and shaking to a mixture of eugenol (54 g.) and ethyl chloroformate (40 g.). The whole was extracted with ether, the extract washed with water and dried, the ether removed, and the residue distilled in a vacuum (50 g., b. p. 135–138°/1.5 mm.). The distillate solidified to stout rhombs, m. p. 31°.

O-Carboethoxyhomovanillin.—O-Carboethoxyeugenol (10 g.) was dissolved in ethyl acetate (100 c.c.), the solution placed in the ozonolysis vessel (see fig.), and the whole cooled in acetone-Drikold. A



stream of 5% ozone at 50 c.c./min. was passed in for 6 hrs. The cold solution of the ozonide was hydrogenated in the presence of palladised charcoal (2 g.); hydrogen being rapidly absorbed (530 c.c. at 17° and 754 mm. in 40 mins.). The flask was evacuated, air admitted, the flask shaken for 10 mins., the air replaced by hydrogen, and the flask shaken for 5 hrs. The solution was filtered (the catalyst, after being washed with a little alcohol and dried, can be used 10–12 times), and the solvent removed under reduced pressure. The residue was dissolved in ether, the solution washed with saturated sodium hydrogen carbonate solution (washings A, see below), dried, the ether removed, and the residue fractionated in a vacuum: 0.5 g., b. p. 135–140°/2 mm.; 7.5 g., b. p. 150–155°/2 mm.; 1 g., b. p. 170–200°/2–3 mm. The redistilled middle fraction was O-carboethoxyhomovanillin (Found: C, 60.7; H, 6.1. $C_{11}H_{14}O_5$ requires C, 60.5; H, 5.9%); its 2:4-dinitrophenylhydrazones formed short yellow needles, m. p. 129–130° (Found: C, 51.7; H, 4.7. $C_{11}H_{10}O_5N_4$ requires C, 51.7; H, 4.3%), from alcohol, and its *p*-nitrophenylhydrazones crystallised from alcohol in orange-red rhombs, m. p. 85–86° (Found: C, 57.6; H, 5.0. $C_{11}H_{10}O_5N_2$ requires C, 57.8; H, 5.1%).

Homovanillin.—Carboethoxyhomovanillin (4.5 g.) was dissolved in absolute alcohol (75 c.c.), and dry hydrogen chloride (1.5 g.) passed in. The whole was heated for 1 hr. at 60°, the alcohol removed under reduced pressure, and the residue dissolved in ether; the ethereal solution was washed with saturated sodium hydrogen carbonate solution, dried, the ether removed, and the residue twice distilled in a vacuum (3.2 g.), b. p. 147–149°/2 mm. (Found: C, 65.5; H, 6.0. Calc. for $C_9H_{10}O_3$: C, 65.2; H, 6.2%). Homovanillin is a pale oil, stable in air, and giving a blue coloration with ferric chloride. Its 2:4-dinitrophenylhydrazones crystallised from alcohol in yellow cubes, m. p. 203°. Its *p*-nitrophenylhydrazones, recrystallised from ethyl acetate, had m. p. 154° (Harries and Haarmann, *loc. cit.*, give m. p. 154–155°). The semicarbazone, recrystallised from alcohol, had m. p. 173° (Harries and Haarmann, *loc. cit.*, give 173°), and the oxime, colourless needles from alcohol, had m. p. 115° (Harries and Haarmann, *loc. cit.*, give 115°).

O-Carboethoxyhomovanillic Acid.—On acidifying the wash liquor (A) from carboethoxyhomovanillin a colourless crystalline solid was precipitated; it recrystallised from water as glistening, colourless, elongated plates of the acid (0.1 g.), m. p. 125–126° (Found: C, 56.5; H, 5.3. $C_{11}H_{14}O_6$ requires C, 56.7; H, 5.5%).

Homovanillic acid. O-Carboethoxyhomovanillic acid (1 g.) was heated for 2 hours on a water-bath with sodium hydroxide (10%, 6 c.c.), and the product, precipitated by acidification and cooling, was recrystallised from water, forming glistening plates (0.7 g.), m. p. 139° (Harries and Haarmann, *loc. cit.*, give 139°).

O-Acetylhomovanillin.—O-Acetyleneugenol (13 g.) was ozonised for 11 hrs. and worked up in the same manner as the carboethoxy-compound (0.6 g., b. p. 139–135°/2 mm.; 9.2 g., b. p. 140–145°/2 mm.; 2 g., b. p. 150–200°/2 mm.). The redistilled middle fraction (Found: C, 63.1; H, 5.6. Calc. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.8%) gave a 2:4-dinitrophenylhydrazone, which crystallised from alcohol in yellow cubes, m. p. 144–145° (Found: C, 52.8; H, 4.3. $C_{11}H_{10}O_7N_4$ requires C, 52.6; H, 4.1%).

O-Acetylhomovanillic Acid.—(1) Homovanillic acid (0.5 g.) was dissolved in a solution of sodium hydroxide (0.3 g.) and poured into acetyl chloride (1 c.c.). The product which separated on cooling crystallised from water in glistening plates (0.45 g., m. p. 135–136°) (Harries and Haarmann, *loc. cit.*, give 134°). Hydrolysis gave homovanillic acid, m. p. and mixed m. p. 139°.

(2) The bicarbonate wash liquor from acetylhomovanillin gave, on acidification and recrystallisation from water, the same acid (0.2 g., m. p. and mixed m. p. 135–136°).

(3) *O*-Acetyl Eugenol (2 g.) in ethyl acetate (100 c.c.) was ozonised for 12 hrs. at 0°. Removal of the solvent, dissolution of the residue in ether, extraction of the ethereal solution with saturated bicarbonate solution, and acidification of the extract gave acetylhomovanillic acid (1.2 g.), m. p. and mixed m. p. 135–136°.

(4) Acetylhomovanillin (2 g.) in acetone (15 c.c.) was shaken with a solution of potassium permanganate (1 g.) in water (1500 c.c.) containing magnesium sulphate (2 g.) for 24 hrs. The manganese dioxide was filtered off, and the filtrate evaporated to dryness. Hydrochloric acid (6*N*, 13 c.c.) was added, and acetylhomovanillic acid filtered off and recrystallised from water (0.8 g.), m. p. and mixed m. p. 135–136°; a small amount of homovanillic acid was also formed.

Vanillic Acid.—Acetylhomovanillin (1 g.) in acetone (30 c.c.) was shaken with potassium permanganate (1 g.) dissolved in water (100 c.c.), the manganese dioxide filtered off, the filtrate evaporated to dryness, and the residue ground with concentrated hydrochloric acid (5 c.c.) and warmed on the water-bath for 15 mins. The vanillic acid was filtered off, and recrystallised from water as lustreless cubes (0.25 g., m. p. and mixed m. p. 207°).

Nitration of *O*-Acetylhomovanillin.—Fuming nitric acid (*d* 1.52, 0.36 g.) was added dropwise to a mechanically stirred solution of acetylhomovanillin (2 g.) in acetic anhydride (25 c.c.) in a freezing mixture, and the whole was set aside overnight. Urea (1 g.) was added, the mixture diluted with water (100 c.c.) and extracted with ether, the extract washed with sodium hydrogen carbonate solution (5%), dried, and the ether removed. The residue was a deep red oil which solidified in "Drikold" but melted again at room temperature; it could not be distilled. Use of twice the quantity of nitric acid and warming the reaction mixture on the water-bath gave an apparently identical product.

***O*-Carbobenzyloxyeugenol.**—Carbobenzyloxy chloride (3.5 g.) (Bergmann and Zervas, *loc. cit.*) was added to a suspension of eugenol (3 g.) in water (70 c.c.) containing sodium carbonate (1 g.). The whole was shaken for 48 hrs., the smell of the acid chloride then having almost gone (cf. Olcott, *loc. cit.*). The suspension was extracted with ether, the extract dried, the ether removed, and the residue distilled in a vacuum (5.8 g., b. p. 170–180°/1–2 mm.). On standing, the distillate solidified into stout needles, m. p. 53°.

***O*-Carbobenzyloxyhomovanillin.**—Carbobenzyloxyeugenol (13 g.) was ozonised for 6 hrs. and worked up in the same manner as the carbethoxy-compound except that 6 g. of palladised charcoal were used. The middle fraction (9 g., b. p. 160–170°/1 mm. Found: C, 67.7; H, 5.5. $C_{17}H_{16}O_8$ requires C, 68.0; H, 5.3%) gave no coloration with ferric chloride.

***O*-Carbobenzyloxyhomovanillic Acid.**—The bicarbonate wash liquor from the last experiment, on neutralisation, gave this acid, which crystallised from water in long lustrous needles (0.8 g., m. p. 107–108°). On refluxing with hydrochloric acid (4*N*, 10 c.c.), this gave homovanillic acid, m. p. and mixed m. p. 139°.

3-4'-Hydroxy-3'-methoxyphenylindole.—Homovanillin (2.2 g.) and phenylhydrazine (1.5 g., freshly distilled) were refluxed in alcohol (25 c.c.) for 3 hrs., and the alcohol distilled off. Fresh alcohol (25 c.c.) was added and the solution saturated with dry hydrogen chloride and refluxed for 1 hr. The alcohol was distilled off, alcohol (25 c.c.) added, and the whole saturated with dry hydrogen chloride at 0° and set aside overnight, then refluxed for 1 hr. and the alcohol distilled off. The residue was extracted with hot benzene, and the extract cooled, filtered, and the benzene removed. The residual oil (0.5 c.c.), dissolved in benzene (0.7 c.c.), was poured dropwise into well-stirred light petroleum (b. p. 40–60°). The creamy-white precipitate was filtered off and washed with a little light petroleum, then recrystallised from benzene-light petroleum (b. p. 80–100°) (0.5 g., m. p. 117°, softening at 100°) (Found: C, 75.1; H, 5.4. $C_{15}H_{13}O_2N$ requires C, 75.3; H, 5.45%). The indole is soluble in alcohol, benzene, acetone, acetic anhydride, and sodium hydroxide solution, and slightly soluble in hot light petroleum. It gives no coloration in the Ehrlich test, but gives a red-violet pine-shaving reaction, and with concentrated sulphuric acid, a blood-red colour, changing to purple and brown. 3-Phenylindole also gives no Ehrlich test, but with concentrated sulphuric acid it gives a yellow colour, changing to red and brown.

The *O*-acetyl derivative, had m. p. 96° (softening at 90°) (Found: C, 70.9; H, 5.1. $C_{17}H_{15}O_3N$ requires C, 71.4; H, 5.6%), and the *O*-benzoyl derivative m. p. 133° (softening at 130°) (Found: C, 78.2; H, 4.5. $C_{22}H_{17}O_3N$ requires C, 78.9; H, 4.95%), both from benzene light petroleum (b. p. 80–100°).

Both compounds were soluble in organic solvents, but almost insoluble in sodium hydroxide solution or water; neither gave an Ehrlich reaction, but both gave a violet colour in the pine-shaving test.

β-4-Hydroxy-3-methoxyphenylalanine.—*O*-Acetylhomovanillin (20 g.) was dissolved in liquid hydrogen cyanide (40 c.c.), and after 10 mins. the solution was slowly added with stirring to a solution of ammonia (20 g.) in water (25 c.c.) cooled to –70°. The result was sealed, and the mixture set aside overnight and then slowly added to a mechanically stirred solution of sulphuric acid (1200 c.c., 40%), heated to 125° for 3 hrs., and poured into water (2 l.). The solution was heated to boiling and barium hydroxide (700 g.) added. Superheated steam was passed through the boiling solution, while barium carbonate was added in small portions till no more ammonia was evolved (ca. 250 g. required). Dilute sulphuric acid was added until the solution showed the presence of sulphate ion, and the barium sulphate was filtered off and well washed, and the combined filtrate and washings concentrated to 100 c.c. The hot solution was treated with lead carbonate until effervescence ceased (ca. 10–12 g.); it was not acid to Congo-red. The whole, after standing overnight, was filtered and the filtrate saturated with hydrogen sulphide, allowed to stand, and refiltered. After being boiled with charcoal (3 g.), the filtered solution was concentrated to 20 c.c. and set aside. The crystals (5 g., and a further 1.4 g. obtained on concentration) melted at 228–229°. Recrystallisation from water afforded colourless needles (4 g.), m. p. 254–255° (decomp.), after losing water of crystallisation (Johnson and Bengis, *loc. cit.*, report a dihydrate, m. p. 255–256°, decomp.).

The anhydrous hydrogen cyanide used was conveniently stored in an equal volume of glacial acetic acid. No heat was evolved on mixing, and the solution was kept in an ordinary well-stoppered bottle without deterioration. The pure cyanide was obtained by distilling the solution from a bath at 30–40°.

2-O-Acetylhomovanillylidene-cyclohexanone (III).—Acetylhomovanillin (13 g.) and cyclohexanone (8 g.) in dry technical pyridine (80 c.c., b. p. 135°) were heated under reflux for 8 hrs., the solvent evaporated off, and the residue poured into water (180 c.c.). The mixture was acidified and extracted with warm benzene, the extract washed (dilute hydrochloric acid; dilute sodium hydroxide solution; water), dried, and refluxed for 0.5 hr. with active charcoal (2 g.). The hot solution was filtered and concentrated to 40 c.c., the residue poured dropwise into well-stirred cold light petroleum (b. p. 40–60°), and the creamy-white precipitate of the compound (III) (18 g.) filtered off, washed with a little petroleum, and recrystallised from benzene–light petroleum or dilute alcohol (10 g.), m. p. 84° (Found: C, 70.5; H, 7.3. $C_{17}H_{20}O_2$ requires C, 71.0; H, 7.0%). The oxime formed needles, m. p. 106°, from alcohol.

2-Homovanillylidene-cyclohexanone.—(1) The above ketone (0.5 g.) was shaken with sodium hydroxide solution (6%, 25 c.c.) at 100° for 0.5 hr., then heated at this temperature for 1 hr. After cooling, the solution was extracted with ether, acidified, and extracted with benzene. The benzene extract was dried and boiled under reflux with active charcoal (0.2 g.) for 0.25 hr. The extract was filtered, concentrated to 4 c.c., and poured dropwise with stirring into cold light petroleum (b. p. 40–60°). The creamy-white precipitate was filtered off and washed with a little petroleum, then recrystallised from benzene–light petroleum or dilute alcohol (0.3 g., m. p. 105°).

(2) **O-Acetylhomovanillin** (3.5 g.) and cyclohexanone (2 g.) were refluxed in absolute alcohol (50 c.c.) containing sodium (2.5 g.) for 4 hrs. Glacial acetic acid (6.5 c.c.) was added, and the alcohol removed. The residue was poured dropwise into well-stirred ice-water, and the precipitate collected, washed, dried, dissolved in benzene (50 c.c.), and worked up as above, giving 3 g., m. p. and mixed m. p. with the above 105°.

2-O-Acetylhomovanillyl-cyclohexanone (IV).—(1) 2-Acetylhomovanillylidene-cyclohexanone (3 g.) was dissolved in alcohol (25 c.c.), and the solution vigorously stirred while sodium amalgam (4%, 40 g.) was added in small portions. The solution was kept just acid by gradual addition of glacial acetic acid (4.5 c.c.). The temperature towards the end of the reaction was kept between 50° and 60°. The whole was made slightly basic (sodium hydroxide) and evaporated to dryness. The residue was extracted with hot benzene, the extract washed with a little water, dried, refluxed with active charcoal (0.8 g.) for 0.3 hr., filtered, concentrated to 8 c.c., and poured dropwise into well-stirred cold light petroleum (b. p. 40–60°). The colourless precipitate was collected, washed with a little petroleum, and crystallised from benzene–light petroleum or dilute alcohol (2.5 g., m. p. 134°).

(2) The same ketone (30.13 mg.) was quantitatively hydrogenated in glacial acetic acid (10 c.c.) with freshly reduced Adams's catalyst (3 mg.), 2.30 c.c. of hydrogen at N.T.P. being absorbed in 20 mins. (0.985 double bond). The solution was filtered and concentrated to 1.5 c.c., water (20 c.c.) was added, and the precipitate recrystallised from benzene–light petroleum, giving 0.02 g., m. p. and mixed m. p. with the above 134°. The compound was saturated and gave an oxime, needles (from alcohol), m. p. 83°.

2-O-Acetylhomovanillylidenecyclohexanol (V).—2-Acetylhomovanillylidene-cyclohexanone (3 g.), dissolved in moist ether (150 c.c.), was heated under reflux for 12 hrs. with freshly prepared aluminium amalgam (4 g.), the mixture filtered, and the alumina and excess of amalgam washed with ether; the filtrate and washings were dried, the ether removed, and the residual oil dissolved in benzene (8 c.c.) and poured dropwise into well-stirred cold light petroleum. The precipitate was collected, washed with a little petroleum, and recrystallised from benzene–light petroleum. The compound (2.4 g., m. p. 151°) was unsaturated and did not form an oxime, but was soluble in sodium hydroxide.

2-O-Acetylhomovanillyl-cyclohexanol (VI).—(1) The above hexanol (36.41 mg.) was quantitatively hydrogenated in glacial acetic acid solution (10 c.c.) with freshly reduced Adams's catalyst (5 mg.); 2.76 c.c. of hydrogen at N.T.P. were absorbed in 15 mins. (0.982 double bond). The solution was filtered and concentrated to 1.3 c.c., water (20 c.c.) was added, and the precipitate recrystallised from benzene–light petroleum (0.02 g., m. p. 171°).

(2) 2-Acetylhomovanillyl-cyclohexanone (3 g.), treated with aluminium amalgam and worked up exactly as in the preparation of (V), gave 2.58 g., m. p. and mixed m. p. with preparation (1) 171°; the compound (VI) was saturated and non-ketonic (Found: C, 70.0; H, 8.0. $C_{17}H_{24}O_2$ requires C, 70.0; H, 8.2%). This gave a benzoate, m. p. 156° (Found: C, 72.4; H, 6.9. $C_{21}H_{28}O_3$ requires C, 72.7; H, 7.1%), from benzene–light petroleum.

Attempted Cyclisations.—(1) **2-Homovanillyl-cyclohexanol.** 2-Acetylhomovanillyl-cyclohexanol (0.3 g.), dissolved in absolute alcohol (10 c.c.) containing sodium (0.2 g.), was heated under reflux for 2 hrs. Glacial acetic acid (1 c.c.) was then added, and the whole evaporated to dryness. The residue was extracted with ether, and the extract washed (sodium carbonate), and dried. The ether was removed, and the oily residue dissolved in benzene (1.5 c.c.) and poured into cold, well-stirred light petroleum (b. p. 40–60°). The precipitate, recrystallised from benzene–light petroleum (0.14 g.), had m. p. 161–163° and was probably 2-homovanillyl-cyclohexanol (Found: C, 72.1; H, 8.5. $C_{17}H_{22}O_2$ requires C, 72.0; H, 8.8%).

(2) The cyclohexanol (0.5 g.) was stirred into syrupy phosphoric acid (3 c.c.) and set aside for 10 hrs. The whole was poured into water, basified (sodium hydroxide), and extracted with ether. This extract contained only a trace of material. The aqueous solution was acidified and extracted with ether, and the extract worked up like the ethereal extract in (1), giving 0.3 g., m. p. and mixed m. p. with the starting material 171°.

(3) The cyclohexanol (0.5 g.) was stirred into syrupy phosphoric acid (3 c.c.) and warmed on the water-bath for 1 hr. Considerable tar was formed. Working up as in (2) afforded only 0.1 g. of starting material.

(4) To the cyclohexanol (0.3 g.) refluxing in benzene (10 c.c.), phosphoric oxide (0.6 g.) was added in small portions during 1.5 hrs. Water (25 c.c.) was added to the cooled reaction mixture, and the whole worked up as above. Only impure starting material (0.1 g.) was obtained.

3-Acetoxy-2-methoxy-9:10-dihydrophenanthrene. (1) 2-O-Acetylhomovanillylidene-cyclohexanone (10

g.) and benzene (100 c.c.) were heated under reflux while phosphoric oxide (10 g.) was added in small portions during 3 hrs. The mixture was decomposed with water (200 c.c.), and the whole basified (sodium hydroxide) and extracted with ether (extract *A*). The aqueous solution was acidified and extracted again with ether (extract *B*). Extract *A* was washed with water, dried, and the ether removed. The residue, recrystallised several times from dilute alcohol, gave needles (0.18 g.), m. p. 174° (Found: C, 75.9; H, 5.66. $C_{11}H_{14}O_2$ requires C, 76.1; H, 6.0%). Extract *B* similarly gave 0.049 g. of leaflets from dilute alcohol, m. p. 147° (compound *H*).

(2) The cyclohexanone (5 g.) was dissolved in chloroform (40 c.c.), and phosphorus oxychloride (6 c.c.) added. The whole was kept overnight, shaken with water, and then with sodium carbonate solution. The chloroform layer was filtered and dried, the chloroform removed, and the residue (ca. 1 g.) dissolved in a little alcohol. The crystals deposited on standing were recrystallised from dilute alcohol, affording needles (0.2 g.), m. p. and mixed m. p. with the above 174°.

The above compound, m. p. 174° (0.05 g.), was heated at 290–300° with selenium (0.1 g.). The sublimate (ca. 0.03 g.), resublimed in a vacuum, had m. p. and mixed m. p. with phenanthrene, 99°; picrate (from alcohol), m. p. 141°.

3-Acetoxy-2-methoxyphenanthrene (VII; R = Ac).—(1) The above dihydro-compound (0.1 g.) was mixed with palladium-black (0.1 g.) and heated at 210–220° until no further change was visible. Alcohol (2 c.c.), was added, the whole warmed and filtered, the filtrate concentrated to 0.3 c.c., and hot water (1 c.c.) added. The crystals which separated on cooling, recrystallised from dilute alcohol, formed needles (0.02 g.), m. p. 144°.

(2) The dihydro-compound (0.3 g.) was heated under reflux for 5 hrs. with maleic acid (0.8 g.), palladium-black (0.25 g.), and water (6 c.c.), diluted with alcohol (12 c.c.), filtered hot, and the filtrate evaporated to dryness. The residue was warmed and stirred with sodium carbonate solution (12 c.c.) and extracted several times with ether, the extract dried, and the ether removed. The residue recrystallised from alcohol in stout, colourless needles (0.2 g.), m. p. 144° (Gilman and Cook, *loc. cit.*, give 146–147°) (Found: C, 74.6; H, 5.6. Calc. for $C_{17}H_{14}O_2$: C, 74.9; H, 5.3%).

3-Hydroxy-2-methoxyphenanthrene. (1) The above acetoxy-compound (0.16 g.) was heated for 2 hrs. with sodium hydroxide solution (8%, 3 c.c.), and the solution acidified, allowed to cool, and filtered. The precipitate recrystallised from dilute alcohol in short needles (0.11 g.), m. p. 143° (Gilman and Cook, *loc. cit.*, give 145–146°) (Found: C, 80.3; H, 5.6. Calc. for $C_{17}H_{14}O_2$: C, 80.5; H, 5.35%).

(2) Compound *H* (above) (0.03 g.) was refluxed for 4 hrs. with maleic acid (0.1 g.), palladium-black (0.05 g.), and water (1.2 c.c.), and the product worked up as above; it gave 0.01 g. of needles, m. p. and mixed m. p. with the above, 143°.

2:3-Dimethoxyphenanthrene. The above hydroxy-compound (0.1 g.) was dissolved in sodium hydroxide solution (3 c.c., 2%), and the solution heated on the water-bath. Methyl sulphate (0.1 c.c.) was added with stirring, and after 0.25 hr., sodium hydroxide solution (3 c.c., 4%) was added, and the whole heated for a further 0.25 hr. The reaction mixture when cold was extracted with ether, and the extract dried. The ether was removed, and the residue recrystallised from dilute alcohol in leaflets (0.08 g.), m. p. 130–131° (Pschorr and Buckow, *loc. cit.*, and Pschorr, *Annalen*, 1912, 391, 39, give m. p. 131°) (Found: C, 80.5; H, 5.7. Calc. for $C_{18}H_{14}O_2$: C, 80.7; H, 5.9%). The picrate separated in yellow needles, m. p. 125–126° (Pschorr, *loc. cit.*, gives 127°).

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[Received, January 20th, 1947.]

NOTES.

Derivatives of Indene and of Butyric Acid. By J. S. H. DAVIES and D. S. MORRIS.

THE work of various authors (*Chem. Reviews*, 1945, 37, 481) has shown that certain derivatives of 6-hydroxy-2-*p*-hydroxyphenylindene and of 6-hydroxy-2-*p*-hydroxyphenyl-3:4-dihydronaphthalene possess oestrogenic activity. Our programme to extend the work of these authors, although well advanced, was anticipated by the publication of Silverman and Bogert (*J. Org. Chem.*, 1946, 11, 34).

The present note deals with two similar indenenes, not previously described, and also with unsuccessful attempts to prepare α -diphenylbutyric acid and α -di-*p*-methoxyphenylbutyric acid from ethyl α -diphenylacetoacetate and its di-*p*-methoxy-derivative respectively, as intermediates in an alternative route to 2-phenyltetralone and 7-methoxy-2-*p*-methoxyphenyltetralone.

6-Methoxy-2-*p*-methoxyphenylindene.—The 6-methoxy-2-*p*-methoxyphenylindanone required was prepared by the route independently used by Silverman and Bogert (*loc. cit.*). The indanone (1 g.) was hydrogenated at ordinary temperature and pressure in ethyl alcohol in presence of Raney nickel (2 g.). The residue obtained after filtration and removal of solvent was stirred with concentrated sulphuric acid (1 drop), warmed for a few minutes on the water-bath, and extracted with benzene. The indene formed small needles, m. p. 194° from alcohol (Found: C, 80.2; H, 6.2. $C_{17}H_{14}O_2$ requires C, 81.0; H, 6.3%).

6-Methoxy-2:3-di-*p*-methoxyphenylindene.—The above indanone (1.5 g.) in toluene (14 c.c.) was added to the Grignard reagent prepared from *p*-anisyl bromide (2.1 g.), magnesium (0.27 g.), and ether (28 c.c.). After the ether had been removed, the toluene solution boiled for 1 hour, and the complex decomposed, the residue from the toluene was dissolved in a mixture of light petroleum (b. p. 40–60°) and benzene (1:1 by vol.) and chromatographed (alumina). Pure 6-methoxy-2:3-di-*p*-methoxyphenylindene (0.7 g.) was obtained as small needles, m. p. 129–130° (Found: C, 80.0; H, 6.4. $C_{24}H_{20}O_2$ requires C, 80.4; H, 6.1%).

β -Hydroxy- α -diphenylbutyric Acid.—Ethyl α -diphenylacetoacetate (28.2 g.), prepared by the

method of Conant and Blatt (*J. Amer. Chem. Soc.*, 1929, **51**, 1227), was hydrogenated in ethyl alcohol at atmospheric pressure and a maximum temperature of 50–60° in presence of Raney nickel; only one molecular proportion of hydrogen was absorbed. Removal of the catalyst and solvent, followed by hydrolysis of the residue by refluxing it for 4 hours with potassium hydroxide (6.5 g.) in 50% aqueous alcohol, furnished a mixture of a neutral substance (3.8 g.), believed to be phenylethyl alcohol, and β -hydroxy- α -diphenylbutyric acid (13.5 g.) which formed needles, m. p. 210°, from aqueous methyl alcohol (Found: C, 75.1; H, 6.6; equiv., 254. $C_{18}H_{18}O_2$ requires C, 75.0; H, 6.3%; equiv., 256).

The application of Rosenmund's procedure (*Ber.*, 1942, **75**, 1850) to ethyl α -diphenylacetoacetate (1 g.) using palladised barium sulphate (1 g.) in acetic acid (100 c.c.) containing perchloric acid (1 drop) in order to effect further reduction was unsuccessful, the products isolated after hydrolysis being β -hydroxy- α -diphenylbutyric acid (0.3 g.), phenylacetic acid (0.7 g.), and a neutral substance, probably phenylethyl alcohol. The hydrogenation of sodium β -hydroxy- α -diphenylbutyrate in water with copper chromite at 200° and 160 atmospheres gave likewise an acidic product consisting almost entirely of phenylacetic acid.

Ethyl ester. The β -hydroxy-acid (10.5 g.) was refluxed for 4 hours in ethyl alcohol saturated with dry hydrogen chloride. The ester was obtained as an oil (9.5 g.), b. p. 158–160°/1 mm., which slowly solidified and melted at 61–62° (Found: C, 76.3; H, 7.3. $C_{18}H_{20}O_2$ requires C, 76.1; H, 7.0%).

All attempts to dehydrate the acid or ester, which included the phosphoric oxide method of Kon and Nargund (*J.*, 1932, 2461) and the xanthate method (Kon and Narracott, *J.*, 1938, 672), were unsuccessful.

Ethyl α -Di-*p*-methoxyphenylacetoacetate.—Following the method of Conant and Blatt (*loc. cit.*), ethyl *p*-methoxyphenylacetate (114 g.) in ether (100 c.c.) was slowly added to a stirred, cold solution of isopropylmagnesium bromide, prepared from isopropyl bromide (123 g.), magnesium (24.3 g.), and ether (200 c.c.). The mixture was stirred at room temperature for 1 hour, refluxed for 4 hours, and left overnight. Propane was evolved during the reaction. After processing, the oil was distilled and the fraction, b. p. 140–150°/0.0001 mm. (56 g.), was collected. This fraction solidified on standing and was crystallised from alcohol to yield the ester as pale yellow needles, m. p. 61–62° (Found: C, 70.4; H, 6.4. $C_{20}H_{22}O_4$ requires C, 70.2; H, 6.4%).

β -Hydroxy- α -di-*p*-methoxyphenylbutyric Acid.—The above ester (4.5 g.) in ethyl alcohol (200 c.c.) was hydrogenated at ordinary temperature and pressure in the presence of Raney nickel (2 g.); only one molecular proportion of hydrogen was absorbed. Removal of the catalyst and solvent gave the crude ester as an oil (4.5 g.). The oil (1 g.) was shaken for 6 hours at room temperature with aqueous sodium hydroxide (20 c.c., 2N) and ethyl alcohol (10 c.c.). The acid (0.4 g.) was obtained as small needles, m. p. 135–136° raised to 138° after crystallisation from benzene-light petroleum (b. p. 40–60°) (Found: C, 68.3; H, 6.6. $C_{18}H_{20}O_5$ requires C, 68.4; H, 6.3%).—BRITISH SCHERING RESEARCH INSTITUTE, BROOK LANE, ALDERLEY EDGE, CHESHIRE. [Received, January 21st, 1947.]

Compounds Related to 2:3-Dimethylpyridine. By AHMED MUSTAFA and MUSTAFA KAMAL HILMY.

(I) **Action of Aromatic Aldehydes on 2:3-Dimethylpyridine.**—(a) *In presence of acetic anhydride.* The following stilbazoles were prepared by refluxing the appropriate benzaldehyde (1 mol.) with 2:3-dimethylpyridine (1 mol.) and acetic anhydride (6 mols.) for 30 hours, followed by steam distillation (cf. Shaw and Wagstaff, *J.*, 1933, 77). **3-Methyl-2-stilbazole**, obtained as colourless crystals from light petroleum (b. p. 30–50°), m. p. 55° (Found: C, 85.8; H, 6.5; N, 7.1. $C_{14}H_{13}N$ requires C, 86.2; H, 6.6; N, 7.2%), was easily soluble in benzene, alcohol, and hot light petroleum (b. p. 50–70°); picrate, yellow needles, m. p. 198° from alcohol. Its 2'-nitro-derivative, pale yellow needles from light petroleum (b. p. 50–80°), m. p. 105° (Found: C, 69.9; H, 5.0; N, 11.7. $C_{14}H_{11}O_2N_2$ requires C, 70.0; H, 5.0; N, 11.7%), was easily soluble in ether and hot ethyl alcohol; picrate, yellow crystals, m. p. 190–191° from alcohol. Its 3'-nitro-derivative, yellow crystals from ethyl alcohol, m. p. 124° (Found: C, 69.7; H, 5.0; N, 11.7%), was difficultly soluble in cold benzene or cold ethyl alcohol; picrate, yellow crystals, m. p. 208–209° from alcohol; and the 4'-nitro-derivative, yellow crystals from alcohol, m. p. 145° (Found: C, 69.7; H, 4.9; N, 11.8%), was soluble in hot ethyl alcohol and hot benzene; picrate, yellow crystals, m. p. 198–199°, from alcohol.

(b) *In presence of water.* The following alkenes were prepared by heating the aromatic aldehyde and 2:3-dimethylpyridine (1 mol. each) with water (4 mols.) in a sealed tube for 10 hours at 170°. The mixtures were not homogeneous at room temperature. The products were treated as in the preparation of the corresponding stilbazoles (Shaw and Wagstaff, *loc. cit.*). They crystallised as pale yellow crystals from ethyl alcohol. **2'-Nitro-3-methyl-2-stilbazolealkene**, m. p. 105° (Found: C, 65.1; H, 5.1; N, 10.5. $C_{14}H_{11}O_2N_2$ requires C, 65.1; H, 5.4; N, 10.9%); **3'-nitro-analogue**, m. p. 131° (Found: C, 65.0; H, 5.3; N, 11.1%); **4'-nitro-isomer**, m. p. 125–126° (Found: C, 65.1; H, 5.4; N, 10.6%).

The above three alkenes (1 mol. each), boiled with acetic anhydride (4 mols.) for 2 hours, afforded the corresponding stilbazoles (mixed m. p.) in almost pure condition.

(II) **Action of Aromatic Aldehydes on 2:3-Dimethylpyridine Methiodide.**—Solutions of equimolecular amounts of the reagents in a minimum of absolute ethyl alcohol, treated with a few drops of piperidine and then set aside at room temperature for some time, deposited crystals of the condensation product; when this was heated at about 260° under reduced pressure, the corresponding stilbazole distilled over (cf. Koelsch, *J. Amer. Chem. Soc.*, 1944, **66**, 2166).

2:3-Dimethylpyridine methiodide, colourless crystals from absolute ethyl alcohol, m. p. 205° (Found: C, 39.0; H, 5.0; N, 5.6; I, 51.1. $C_8H_{10}NI$ requires C, 38.5; H, 4.8; N, 5.6; I, 51.0%), easily soluble in cold water and soluble in ether, afforded **4'-methoxy-2-methyl-2-stilbazole methiodide**, yellow needles from water, m. p. 234° (decomp.; orange melt) (Found: C, 52.4; H, 4.9; N, 3.7; I, 34.2. $C_{14}H_{15}ONI$ requires C, 52.3; H, 4.9; N, 3.8; I, 34.6%), readily soluble in hot water and practically insoluble in benzene and light petroleum (b. p. 30–50°). The corresponding stilbazole formed almost colourless crystals from light petroleum (b. p. 50–70°), m. p. 88° (Found: C, 79.7; H, 6.7; N, 6.2. $C_{14}H_{15}ON$

requires C, 80.0; H, 6.6; N, 6.2%); it was soluble in ethyl alcohol; picrate, yellow crystals, m. p. 196–197° from ethyl alcohol.

2'-Methoxy-3-methyl-2-stilbazole methiodide formed yellow crystals from water, m. p. 205° (decomp.) (Found: C, 52.3; H, 4.8; N, 3.7; I, 35.0%), and the stilbazole separated in colourless crystals from light petroleum (b. p. 30–50°), m. p. 60° (Found: C, 79.6; H, 6.5; N, 5.9%); picrate, yellow crystals from alcohol, m. p. 208–209°.

3'-Nitro-3-methyl-2-stilbazole methiodide, pale yellow crystals from water, m. p. 245° (decomp.) (Found: C, 44.9; H, 4.4; N, 6.7; I, 32.1. $C_{18}H_{15}O_2N_2I \cdot H_2O$ requires C, 45.0; H, 4.3; N, 7.0; I, 31.7%), difficultly soluble in cold ethyl alcohol and light petroleum (b. p. 30–50°), afforded the stilbazole as yellow crystals from light petroleum (b. p. 90–100°), m. p. 124° (Found: C, 69.5; H, 5.2; N, 11.6%), identical (mixed m. p.) with the specimen described in (I).

3-Methylpiperolidine-2-picoline methiodide, yellow crystals from hot water, m. p. 260° (Found: C, 50.4; H, 4.5; N, 3.7; I, 33.0. $C_{18}H_{15}O_2NI$ requires C, 50.4; H, 4.2; N, 3.7; I, 33.3%), almost insoluble in light petroleum (b. p. 50–70°), afforded the base as almost colourless crystals from light petroleum (b. p. 90–100°), m. p. 117° (Found: C, 75.0; H, 5.4; N, 6.1. $C_{15}H_{13}O_2N$ requires C, 75.3; H, 5.4; N, 5.9%), soluble in hot ethyl alcohol or benzene; picrate, yellow crystals, m. p. 219° (decomp.), from ethyl alcohol.

4'-Dimethylamino-3-methyl-2-stilbazole methiodide, reddish silky crystals from hot water, m. p. 255° (decomp.) (Found: N, 6.9; I, 33.0. $C_{18}H_{19}N_2I$ requires N, 7.4; I, 33.4%), almost insoluble in cold water and in light petroleum (b. p. 30–50°), afforded the stilbazole as golden-yellow needles from ethyl alcohol, m. p. 93° (yellow-brown melt) (Found: C, 80.5; H, 7.5. $C_{18}H_{19}N_2$ requires C, 80.7; H, 7.5%), soluble in benzene and hot light petroleum (b. p. 80–90°); picrate, brick red crystals, m. p. 202° (red melt) from ethyl alcohol.

(III) Action of Alcoholic Potassium Hydroxide on Stilbazoles.—4'-Nitro-3-methyl-2-stilbazole (1 g.) and ethyl alcoholic potassium hydroxide (15%; 10 c.c.) were heated at 100° for 15 minutes; the crystals which separated were filtered off, washed with water, and crystallised from benzene, forming golden-yellow crystals, m. p. 220° (red melt) (Found: C, 78.2; H, 5.6; N, 13.3. $C_{22}H_{14}ON_4$ requires C, 77.8; H, 5.5; N, 13.0%). 4'-Azoxy-3-methyl-2-stilbazole was difficultly soluble in ethyl alcohol and gave a deep red colour with concentrated sulphuric acid. Similarly, the 3'-azoxy-compound was obtained as brown crystals from benzene, m. p. 157° (Found: C, 78.2; H, 5.3; N, 12.9%), difficultly soluble in cold ethyl alcohol and giving a red colour with sulphuric acid; and the 2'-azoxy-isomer formed pale yellow crystals, from benzene, m. p. 174° (Found: C, 78.3; H, 5.6; N, 12.7%), difficultly soluble in ethyl alcohol and giving an orange-red colour with sulphuric acid.—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA-CAIRO, EGYPT. [Received, January 27th, 1947.]

The Infra-red Spectrum of Vulcanised Rubber and the Chemical Reaction Between Rubber and Sulphur.

By N. SHEPPARD and G. B. B. M. SUTHERLAND.

IN an earlier paper (*Trans. Faraday Soc.*, 1945, **41**, 261) we described an infra-red spectroscopic investigation of the vulcanisation of rubber, and drew attention to a band at 10.4μ (960 cm^{-1}) which appeared in the spectrum of both straight and accelerated vulcanisation. We have further investigated this phenomenon and find that the intensity of this band correlates well with the amount of sulphur chemically incorporated, but not with the degree of vulcanisation as reflected in the physical properties of the finished product.

We were unable to explain this band in a convincing manner in terms of C-S linkages, but more recently have found a band in the same position (10.4μ), and another at 11.2μ (890 cm^{-1}) in certain thermally degraded rubbers. Since in this case the two new bands are obviously due respectively to the development of new CHR:CHR', and CRR':CH₂ groups, it seemed probable that the 10.4μ band in vulcanised rubber might also be caused by new groupings of the former type. An investigation of the spectrum of an ebonite (in which the rubber-sulphur reaction has been carried to an extreme) gave confirmation of this idea. In this spectrum, absorptions in the region of 6μ showed that a considerable number of double bonds remained, but the characteristic absorption at 12.0μ arising from CRR':CHR' groups in rubber had largely disappeared. On the other hand the band at 10.4μ (although now shifted to slightly longer wave-lengths) had greatly increased in intensity.

These facts find a convincing explanation in the hypothesis that the reaction between rubber and sulphur causes at some stage a shift in the position of the double bond of type —CMe:CH— in the rubber chain, giving rise to a group of the type CHR:CHR. Further confirmation of this comes from the studies of Farmer and Shipley (this vol. p. 1519) on the reaction between sulphur and the diolefins, geraniolene and dihydromyrcene. The available data on the structures of these reaction products have led these authors to conclude that α -methylene initiation of the sulphuration reaction occurs to an important extent.

They envisage attack of the $-\overset{1}{\text{CH}_2}-\overset{2}{\text{CMe}}:\overset{3}{\text{CH}}-\overset{4}{\text{CH}_2}-$ group which is common to rubber and the diolefins at positions (1) or (4) with the initial removal of a hydrogen atom from the α -methylene carbon atoms. The radical formed by removal of a hydrogen atom from (1) could by resonance cause the double bond to move to the left. In this new position the double bond would still be of type CRR':CHR' and would be expected to absorb at the usual 12.0μ position. However, removal of the hydrogen atom from (4) would give rise to a radical which could move the double bond to the right and thus give rise to CHR:CHR' groups, and hence to a band at 10.4μ in the final product.

The work described above on the vulcanisation and degradation of rubber will be published in more detail later. We should like to express our thanks to Dr. E. H. Farmer and Dr. R. F. Naylor for helpful discussions on the above points.—THE LABORATORY OF COLLOID SCIENCE, CAMBRIDGE. [Received, March 24th, 1947.]

The Ernst Julius Cohen Memorial Lecture.

DELIVERED BEFORE THE CHEMICAL SOCIETY ON OCTOBER 2ND, 1947.

By F. G. DONNAN, C.B.E., D.Sc., LL.D., F.R.S.

AMONGST the distinguished Dutch men of science of the generation that is now passing, or has already passed, away, a very high place must, by universal consent, be assigned to the subject of this Memoir. It would be no exaggeration to say that the name, and very often the personality, of Ernst Cohen have been known to students of chemistry and physics throughout the world for nearly fifty years. His famous researches in the fields of polymorphism, electrochemistry, thermochemistry, and piezochemistry, the excellent books he wrote, his many visits to other countries and the lectures he gave therein, and—last but not least—the important part he played in the national and international organisation and development of chemical science, made Ernst Cohen one of the most outstanding and well beloved men of science of his day and generation.

He was the devoted pupil and disciple of the great van't Hoff, and belonged to that famous Dutch school of physicochemical science associated with the names of van't Hoff, Roozeboom, Cohen, and Schreinemakers. Although van't Hoff is, perhaps, best known to students of chemistry for his pioneer work on optical activity and the "tetrahedral carbon atom", the laws of osmotic pressure, and the application of thermodynamics to the study of chemical equilibria and "chemical dynamics", he became interested in the conditions of formation and decomposition of double salts before he left Amsterdam, and during his Berlin period (from 1895 onwards) devoted himself to the study of the formation of oceanic salt deposits. The famous work of Roozeboom on "Heterogene Gleichgewichte" is well known to physical chemists and metallurgists, whilst Schreinemakers, the mathematician and geometer, became the great investigator and exponent of "geometrical" thermodynamics as applied to the transformations and equilibria of heterogeneous multicomponent systems. Broadly speaking, we may say that Cohen took a line of his own, and devoted a large proportion of his researches to the investigation of the polymorphism of one-component systems: the conditions of equilibrium, the transitions, and the stable and metastable states of the various solid (crystalline) modifications of chemically pure substances, especially the elements. His work was characterised by the use of exact electrochemical and thermochemical methods, and by the study of equilibria and transformations at high pressures (up to 1500 atmospheres). Apart from these extensive "piezochemical" researches, he made a long-continued and intensive study of electrochemical thermodynamics, especially in relation to the study of standard galvanic cells (so-called "normal elements").

Ernst Cohen may well be regarded as the greatest of the disciples of van't Hoff. His thesis for the doctorate in Amsterdam under van't Hoff (1893) was probably the starting point, perhaps indeed the fundamental stimulus, of much of his subsequent research work. It was entitled "The Electrical Method of determining Transition-points and the Electromotive Force of Chemical Reactions". If under a given external pressure a chemical reaction be conducted isothermally and reversibly it will yield the maximum external work possible under these conditions. This maximum work, according to van't Hoff, measured the "affinity" of the reaction. Hence the importance of determining the reversible E.M.F. of a galvanic cell in which a chemical reaction occurs isothermally and reversibly, for in this case the maximum work per unit reaction can be calculated. So in his thesis for the doctorate Cohen entered the field of electrochemical thermodynamics, a subject which he developed throughout a long series of researches and which underlay his very important and detailed work on standard cells and other galvanic combinations. It may not be unnecessary to remark that, as probably every student knows now-a-days, the fundamental principles of electrochemical thermodynamics were established by Willard Gibbs in the period 1876—78. We may indeed say that the general *physical* theory underlying the researches of Cohen on the polymorphism and equilibria of solid phases of one-component systems and on galvanic cells, namely the principles of thermodynamics as applied to heterogeneous systems (*i.e.*, multi-phase systems), were established by Willard Gibbs. It is well known that van der Waals directed the attention of Roozeboom to this earlier work of Gibbs, and it is also well known that this indebtedness of the famous Dutch school has been very generously acknowledged. Needless to say, in mentioning the work of Gibbs there is no intention to underrate in the slightest degree the originality and the great scientific value of the work of van't Hoff, Cohen, Roozeboom, and Schreinemakers.



ERNST JULIUS COHEN.

[To face p. 1700.]

Ernst Julius Cohen was born in Amsterdam on March 7th, 1869. It is in the highest degree probable that he would, in normal circumstances, be alive to-day. But, alas, the circumstances were terribly and horribly abnormal. Owing to the fact that he was a man of Jewish descent, it is now a practical certainty that he was foully murdered on or about March 5th, 1944, in a gas chamber at the "extermination" camp of Auschwitz. Concerning this tragic event something more will be said at the conclusion of this Memoir.

Chemistry was in his blood, for his father, Jacques Cohen, born at Düsseldorf in 1833, studied under Liebig at Giessen and afterwards under Bunsen at Heidelberg, where in 1853 he obtained his doctorate in chemistry. Having held posts in technical chemistry at Brussels and Amsterdam, Dr. Jacques Cohen, together with several friends, formed in 1864 the "Company for Chemical Industry" (the Netherlands Coal Tar Distillery), of which he remained Director until his death in 1881. He married in 1863 Johanna Rosenthal, a native of Hanover. Both Jacques Cohen and his wife became Dutch by naturalisation. Ernst Julius was the third of their children.

At the secondary school (Hoogere Burgerschool) in Amsterdam the young Ernst studied chemistry and took a great interest in photography, for which the summer holidays, often spent with his parents in Switzerland, gave him plenty of opportunity. His earliest publications dealt with subjects relating to the art and science of photography. After the school "passing-out examination" came the preparation for the State examination giving access to the University. During this period he was fortunate to obtain excellent private lessons in Latin and Greek from Dr. J. S. Speyer, teacher at the Amsterdam Gymnasium (higher secondary school) and later Professor at Leiden University. This classical and literary training was invaluable to him in later years. In June 1888 he passed the State examination and was then able to devote himself to the study of the exact sciences at the University. The lectures of van't Hoff, van der Waals, and Korteweg particularly attracted him, and with Dr. Ch. M. van Deventer (one of van't Hoff's assistant) he made an investigation of heats of solution. Having passed the "Candidate Examination" in 1890 he went, on van't Hoff's advice, to Paris and worked for a short time in the laboratory of Moissan (then very famous for his isolation of fluorine in 1886). Armed with introductions from van't Hoff, he also visited Berthelot, Pasteur, and Gabriel Lippmann, and saw something of their work and their laboratories. Professor Marey also showed him his photographs of animals in motion. Returning to Amsterdam, he soon afterwards spent some time at the State Agricultural Experimental Station at Breda, where he acquired valuable experience in analytical chemistry. Then came the preparation for the "Doctoral Examination" at the University and attendance at the senior lectures of van der Waals and van't Hoff. This examination was successfully passed in November 1892.

The young candidate for the Doctorate had now to choose the subject for his Doctor thesis. Apparently his reading of van't Hoff's "*Études de Dynamique Chimique*" induced him to request of his prospective sponsor permission for an investigation of the electromotive force resulting from a chemical reaction. Van't Hoff agreed—but with a warning about the difficulties. However, all went well in the end, and on November 8th, 1893, Cohen attained the doctorat in chemistry with honours. The title of his thesis has already been given (see p. 1700).

With his appointment as a demonstrator in van't Hoff's laboratory, there now began a very strenuous period of teaching and research, lasting nine years. Shortly after graduation he married Miss Louise Gompertz, who greatly contributed to the happiness of his home life and the efficiency of his University work. Van't Hoff's new laboratory at Amsterdam became a very active centre of research. In the old laboratory Arrhenius and Meyerhoffer were already working, and to the new laboratory came many men whose names became well known in chemical science—W. D. Bancroft, H. C. Jones, R. Löwenherz, V. Rothmund, and J. Verschaffelt.

Ernst Cohen soon became a Lecturer (Privat Dozent) and a very active and successful investigator. In collaboration with Bredig and van't Hoff he continued the work on "transition elements", and published several papers on subjects related to his interest in photography, e.g., the action of hydrogen on silver bromide gelatine plates; the solubility of silver halides in various solutions; the supposed influence of gelatine on the double decomposition of salts.

A great change came in the Amsterdam laboratory when, in 1895, van't Hoff resigned, and was succeeded by Bakhuis Roozeboom. Cohen now took a much greater part in the lectures on physical chemistry, but this did not interfere with his output of research. Besides work on the decomposition of arsine and on the ionisation of substances in alcohol-water mixtures, his famous series of investigations on the allotropic modifications of tin began, at first in collaboration with van Eijk, whose attention had been drawn to this problem by Roozeboom.

Cohen's reputation as a physical chemist had now risen so high that in 1898 he was offered

the Chair of Physical Chemistry at McGill University in Montreal. He was, however, so happy in Amsterdam and his relations with Roozeboom were so friendly that he declined the honour. In 1901 he became "extraordinary" Professor of Chemistry in the University of Amsterdam, with special reference to Physical Chemistry.

His reputation as a physical and inorganic chemist was now established, with the result that in 1902 he was appointed to the Professorship of Inorganic and General Chemistry at the University of Utrecht. At first he had to occupy the old and very inadequate laboratory which dated from the time of G. J. Mulder. But he had accepted the Chair at Utrecht on the condition that a new laboratory should be built. The new and excellent laboratory, built to his own designs and named the van't Hoff Laboratory in honour of his great teacher and inspirer, was opened on May 18th, 1904, with van't Hoff himself as the guest of honour.

Now began the great period of his life as Professor at Utrecht and Director of the van't Hoff Laboratory, a period which lasted until his retirement in 1939. During this period of thirty-five years he built up one of the world's great centres of teaching and research in physical chemistry. However, it might have happened that Utrecht soon lost Cohen, for, after he had been only five years there, Roozeboom died (1907), and the Professorship at Amsterdam became vacant. It was offered at first to Schreinemakers, who declined. Then the invitation came to Cohen. But he was so happy in his new laboratory and amongst his new colleagues that he also declined the honour.

A very large proportion of the researches in Utrecht due to Cohen and his collaborators and students dealt with the polymorphism of substances, both elements and compounds. The work on tin, begun in Amsterdam, was continued and much developed. This is perhaps the most famous of all his investigations. It had been known before his time that certain organ pipes made of tin in the old castle church at Reitz had largely crumbled into a grey powder during a cold winter (as reported by G. L. Erdmann in 1851), and Fritzsche in 1869 had described a case where blocks of Banca tin had similarly "decayed" in the store of a custom house in Russia. These extraordinary phenomena were explained by Cohen, who showed that they were due to the transformation of ordinary "white" tin into another modification, "grey" tin. By dilatometric and other methods he found the transition temperature to be 18° (corrected later to 13.2°). Below this equilibrium temperature, ordinary white tin is unstable with regard to the stable modification, *i.e.*, the grey tin. But under ordinary conditions the change does not occur, the white tin being then "metastable". The change may, however, be greatly accelerated by various means, *e.g.*, lowering of temperature, presence of certain solvents, "inoculation" with grey tin, etc. Cohen drew attention to the fact that objects of tin kept in museums sometimes develop warty "intumescences", owing to the gradual and local onset of the change to grey tin. He called this the "museum disease", and such changes became celebrated as the "tin disease".

The next case he investigated was the phenomenon known as "explosive antimony". If a concentrated solution of antimony chloride in water (plus some hydrochloric acid) be electrolysed with an antimony anode and a platinum cathode, the metallic deposit on the cathode, if scratched or struck, shows a sudden large evolution of heat, accompanied by clouds of white fumes. Cohen showed that this phenomenon is due to the fact that the original metallic deposit is an unstable (*i.e.*, metastable) modification which changes with evolution of heat to a stable modification, the clouds being caused by the volatilisation of occluded antimony chloride.

He was now well embarked on his great series of investigations of the "physical metamorphosis" (as he called it) of solid substances. In the case of tin, the grey tin is (at ordinary atmospheric pressure) stable below the corresponding transition temperature, the white tin stable above it. This is a case of *enantiotropy*, the two forms being *enantiotropic*. In the case of antimony, one modification has no temperature region of true stability (always metastable). This is an example of *monotropy*. In a long series of researches these phenomena of polymorphism of solid (crystalline) substances were investigated in numerous instances—phosphorus, tellurium, cadmium, bismuth, zinc, copper, the "explosive" platinum metals of Bunsen, lead, silver, potassium, sodium, antimony iodide, cadmium iodide, silver iodide, thallous picrate, ammonium nitrate, etc.

Special attention was paid to the existence of metastable phases and to their usual formation under conditions where the stable ones would be "thermodynamically" expected. The phenomena of both enantiotropy and monotropy were found to be exceedingly common amongst both elements and compounds. From 1909 onwards a series of papers entitled "The metastability of our metal world on account of allotropy, and its significance for physics, chemistry, and technology" were published by Cohen, who had gradually come to the conclusion that most

metals in common use were, if not entirely metastable, at least mixtures of stable and metastable forms (phases). The same thing applied to the majority of solid non-metallic substances. He was also forced to the conclusion that the well-known tables of physical constants, *e.g.*, density, specific heat, etc., contained unreliable data owing to the *physical* "impurity" of solid chemically pure substances.

Reference may be finally made to Cohen's investigations of what he called the "strain disease". Cold working, especially polishing, of metals produces, according to him, metastable conditions as a result of partial disruption or deformation of crystalline structures and the formation of "amorphous" states which, owing to vibration or other causes, are liable to a sort of "recrystallisation", *i.e.*, reversion to the stable crystalline state (compare the "flowed" state of Beilby). Hence the technically troublesome phenomenon of "season cracking".

In his work on the transformation of solid substances from one stable phase to another one, stable at higher temperatures, a very characteristic feature of Cohen's researches was the employment of what he called "transition elements". Various types of such galvanic cells were used, of which a few examples may be mentioned here. If the E.M.F. of the cell

Metal <i>M</i> in the <i>stable</i> solid phase	A solution of a salt of <i>M</i>	Metal <i>M</i> in the <i>metastable</i> solid phase
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be measured at a constant pressure but at different temperatures, it will have a zero value at the transition temperature (equilibrium temperature). The transition cell

Metal <i>M</i> in the <i>stable</i> solid phase	A solution of a salt of <i>M</i>	An amalgam electrode of the metal <i>M</i>
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will show a break in the curve relating E.M.F. to temperature at the transition temperature, provided that the amalgam suffers no change of condition (such as a change from a purely liquid to a heterogeneous state, or vice versa), and that the phase change of *M* is not retarded.

The cell (analogous to the standard Clark cell)

Zinc amalgam	Saturated solution of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ in contact with the solid salt	$\text{Hg}_2\text{SO}_4 \cdot \text{Hg}$
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will show a break in the E.M.F.-temperature curve when the solid heptahydrate changes to the solid hexahydrate.

A study of galvanic cells led him to a long series of researches on the electrochemistry of the standard Clark and Weston cells, including also the Daniell cell and the calomel cell of Lipscomb and Hulett. A close and accurate investigation of all the actions occurring in such cells and the conditions of stability or metastability of all the phases present, whether solid metals, metallic amalgams, or solid salts, led to great and important advances, including, for example, the demonstration that the standard Weston cell (as then employed) was quite unreliable. This close and accurate analysis enabled him to determine with high precision the various quantities occurring in the Gibbs-Helmholtz equation. His work in this field was indeed a most valuable contribution to electrochemical thermodynamics.

An important part of the researches carried out in the Utrecht laboratory by Cohen and his collaborators concerned the effect of pressure on the reactions and equilibria occurring in condensed (liquid and solid) systems. To this branch of chemical science he gave the name "piezochemistry". An account of the work carried out in this field up to 1914 was published by Cohen and Schut in a book entitled "*Piezochemie kondensierter Systeme*" (Leipzig, 1919). This valuable work contained detailed references to the existing scientific literature. An excellent and detailed account of his researches in piezochemistry (up to 1925) can be found in his book entitled "*Physico-chemical Metamorphosis and some Problems in Piezochemistry*" (McGraw Hill, 1928), which contains the twenty-one lectures which he delivered at Cornell University as the George Fisher Baker Non-Residential Lecturer (1925-26). It may be said in passing that anyone wishing to obtain a first-hand and detailed account of Cohen's principal fields of research may be referred to this book.

The elaborate high pressure apparatus constructed in the Utrecht Laboratory enabled measurements to be made up to 1500 atmospheres. A mere enumeration of the principal types of effects which were studied will indicate the extent of this work. These included the effect of pressure on: (1) rates of chemical reaction; (2) transition temperatures of solid phases; (3) electromotive force of galvanic cells; (4) solubilities of solid substances; (5) Faraday's first law; (6) velocity of diffusion in liquid systems; (7) viscosity of liquids; and (8) electrical conductivity of solutions. So great was the extent and detail of these investigations that only a few remarks

can be made on an occasion such as the present. The rate of inversion of sucrose at 25° in an aqueous hydrochloric acid solution was found to be reduced by about 26% when the pressure is increased from one to 1500 atmospheres. In the hydrolysis of ethyl acetate by sodium hydroxide in aqueous solution a rise of pressure from one to 1500 atmospheres increased the reaction-velocity constant by 37%. In these and other similar cases of reaction-velocities the measured effects could not be related to thermodynamical equations dealing with equilibrium states. In the case, however, of transition temperatures of solid phases, use could be made of the well-known Clapeyron equation

$$\frac{dT}{dp} = \frac{T(v_2 - v_1)}{q},$$

where $v_2 - v_1$ denotes the volume change, T the transition (equilibrium) temperature, p the pressure, and q the corresponding heat absorption. In connection with the effect of pressure on solubility, Cohen was able to relate his experimental data to the thermodynamical equation known as "Braun's law", namely

$$\left(\frac{\partial x}{\partial p}\right)_T \bigg/ \left(\frac{\partial x}{\partial T}\right)_p = -T\Delta v/Q,$$

where x denotes the solubility (as moles of solute in a given mass of solvent). On the right-hand side of the equation, Δv denotes the so-called "fictitious" volume change, *i.e.*, that corresponding to the solution of one mole of the solute in a large quantity of the saturated solution at T and p , and Q the corresponding amount of heat absorbed under such conditions, *i.e.*, the "fictitious heat of solution". These fictitious quantities are simply the *limiting* values approached as the concentration of the solution approaches the saturation (equilibrium) value at the given p and T . A fuller and more precise discussion of these matters and a mathematical proof of Braun's equation would have been desirable, but the foregoing remarks must suffice for the purpose of indicating the general nature of Cohen's work in this particular field of investigation.

The measurement of the effect of pressure on the E.M.F. of a reversible galvanic cell at constant temperature enabled Cohen to ascertain the effect of pressure on the "affinity" (in the sense of van't Hoff's definition) of the chemical reactions occurring in the cell, and led him to a very interesting series of investigations (which included measurements of the effect of pressure on the Clark and Weston cells and the lead accumulator). In connection with his work on the effect of pressure on diffusion velocity, a brief reference may be made to the potentiometric measurement of the rate of diffusion of cadmium into mercury. It was found that the velocity of diffusion of cadmium into mercury at 20° is reduced by 5% on application of an external pressure of 1500 atmospheres. Measurements of the viscosity of mercury (at 20°) at pressures of one atmosphere and 1500 atmospheres led Cohen to the conclusion that the product of the diffusion velocity and the viscosity is equal to a constant *independent* of the pressure. Finally, it may be mentioned that he proved experimentally that the electrical charge of an ion in solution is unchanged by an increase of pressure up to 1500 atmospheres.

This brief sketch of some of the main lines of investigation carried out by Cohen and his collaborators might be much extended, did space permit. For example, much excellent calorimetric work on specific heats of solids and solutions and on heats of solution deserves mention, especially the very interesting investigation on the (negative) heats of solution of the various polymorphic forms of cadmium iodide, and their mixtures, which was made possible by the use of a specially constructed and very accurate form of electrical adiabatic calorimeter. Many other lines of work would be worthy of discussion, but the mere mention of a few of them must suffice: osmotic pressure and its measurement; corrosion of metals; effect of traces of water on equilibria in solutions, and superheating in relation to the intensive drying of liquids; influence of dispersity on solubility and physico-chemical constants; velocity of polymorphic changes and the influence of mechanical deformation; polymorphy of ice at one atmosphere pressure.

A very characteristic part of the many activities of Ernst Cohen was due to his deep interest in the history of science, especially, of course, chemical science. Anyone visiting his laboratory or his home was at once struck by the abundance of old prints relating to personalities and events of interest or importance in this history. In his own country he was the moving spirit in the establishment of the historical Committee of the Dutch Chemical Society and the formation of its valuable historical library. He was also one of the founder members of the Dutch Society for the History of Medicine, Natural Sciences, and Mathematics, becoming its Chairman in 1916. A long series of "chemical-historical" articles and notes in the *Chemisch Weekblad* bear ample

witness to his activity in historical research, as do also various books, namely one on the history of "laughing" gas, one on Herman Boerhaave, and his great book on the life and work of van't Hoff.

For a man so actively engaged in the laboratory, his scientific-literary output of books was quite remarkable. In addition to those to which reference has been made, the following may be mentioned: "Studien zur chemischen Dynamik" (an enlarged edition of van't Hoff's "Études de Dynamique Chimique"); Monograph on Tin in Abegg's "Handbuch der anorganischen Chemie"; two textbooks for medical students, one on physical chemistry, and one (with van Romburgh) on inorganic chemistry.

In the field of national and international organisation and co-operation in science, Ernst Cohen took an active and distinguished part. He was a member of the original executive Committee of the Dutch Chemical Society (founded in 1903), and became its first President. He took a very active share in the work of this Society, becoming President again ten years afterwards and finally Honorary President. Elected a member of the Royal Netherlands Academy of Sciences in 1913, he did much to promote the scientific work, organisation, and prestige of this famous Academy. He became a member, and subsequently Chairman, of the Dutch Committee on Coinage. In the international field he took an active part as a member of the Council of the International Union of Pure and Applied Chemistry, becoming President of the Union in succession to Sir William Pope. For many years he was a valuable member of the International Committee responsible for the annual tables of physical and chemical constants. It is no exaggeration to say that as time went on he became one of the great cosmopolitan representatives of chemical science. Invitations to give lectures came to him from many countries. These lectures were very successful, for he was not only a good lecturer but a good linguist, speaking fluent English, French, and German. In this country he delivered the Kamerlingh Onnes and Messel lectures, and also a number of other lectures during his frequent visits to London, Oxford, and Cambridge. Perhaps the most famous—certainly the most extensive—visit was one to Cornell University in the second semester of 1925—26, when he gave a course of twenty-one lectures, as Non-Resident Lecturer in Chemistry on the Baker Foundation. Besides such invitations for special lectures, he took part on various occasions in the meetings of the Faraday Society, the German Bunsen Society, the German Naturforscherversammlung, and many similar societies. So high indeed was his position in the esteem of chemists throughout the world that it would scarcely be possible on the present occasion to enumerate the many invitations he received to visit various countries for special ceremonies. Perhaps it may be permissible to make one exception, namely his visit to Liverpool in 1906 on the occasion of the opening ceremonies of the Muspratt Laboratory of Physical and Electro-Chemistry.

Honours came to him from many countries. It is pleasant to remember that in this country he was elected a Foreign Member of the Royal Society, an Honorary Fellow of the Chemical Society, and an Honorary Member of the Royal Institution.

One of the greatest things Cohen did in the cause of international friendship and co-operation was the famous meeting at Utrecht in the summer of 1922. When staying with Donnan in 1920, the suggestion was made by the latter that it would be a fine thing if an international meeting of chemists could be held in some "neutral" country, preferably Holland. This idea was eagerly taken up by Cohen, who, ably assisted by his colleague, Professor van Romburgh, formed a small international Committee to discuss the matter. This Committee, consisting of E. Biilmann (Copenhagen), G. Bruni (Milan), Victor Henri (Zürich), R. Schenck (Münster), Paul Walden (Rostock), and R. Wegscheider (Vienna), together with Cohen, van Romburgh, Kruyt, and Donnan, met at Cohen's house in 1921. Invitations to 100 chemists in many countries were issued in March 1922, and the great Reunion was held at Utrecht during June 21st—23rd, 1922. Unfortunately, no Belgians or French were present, but from Germany came Bodenstein, Bredig, Hahn, Pfeiffer, Schlenk, Schenck, Stock, Walden, and Wieland. Cohen opened the meeting with words of warm welcome (in five languages), many scientific lectures were held, and magnificent hospitality was provided by our generous Dutch hosts. The Utrecht Reunion was a great success, and a very splendid and noble deed in the cause of international friendship on the part of Dutch men of science.

Ernst Cohen was a man of firm and sincere character, who had many friends in the world of science. The writer of this Memoir met him first in 1904 and was privileged to enjoy his friendship for thirty-five years. His equable and kindly, though serious, temperament, his dry wit and good-natured humour, his constant regard for the wishes and wants of others—all these qualities endeared him to his friends. He was very methodical and systematic in his ways of life, which was one of the secrets of his huge accomplishment of work. He was thrice married,

and is survived by his third wife, née Miss W. A. T. de Meester (now Mrs. van Ginneken-de Meester). His friend and colleague, Professor H. R. Kruyt, has written an appreciation of Cohen's personal qualities as a University teacher and director of research. He possessed in high measure the power of inspiring and guiding his research students and collaborators. Great freedom of thought and initiative were encouraged by the director, but if necessary one had to defend one's point of view by reasoned argument. The result was a happy and co-operative band of successful workers. So great was the number of his research collaborators and assistants that only three can be mentioned here, namely, Miss W. A. T. de Meester (who later became his wife), H. R. Kruyt, and A. L. Th. Moesveld. As is well known, H. R. Kruyt later became a University Professor and colleague of Cohen at Utrecht, and created in the van't Hoff laboratory a famous school of teaching and research in colloid chemistry.

The tragic end of Cohen's life has been described by Kruyt in the *Chemisch Weekblad* (1945, 41, 126—128). In 1941 his property was seized and in April 1942 his house was taken for German officers, but fortunately friendly neighbours took Cohen and his wife into their house. In May 1942 he was obliged to wear the "yellow star" and became subject to the restrictions imposed on Jews. Matters came to a head in 1943, when on a visit to the laboratory he was arrested and taken to a prison in Amsterdam, the charge being that he had entered a "public" building. The many efforts of his friends to secure his release were unavailing, and Cohen was sent to the concentration camp at Vught in Holland. At a discussion of this state of affairs by the Council of the Dutch Chemical Society, it was proposed by Dr. Kappelmeier that an approach be made to the S.S. authorities at the Hague. This was successful, Cohen was released, and soon afterwards was freed from practically all the restrictions imposed on Jews. But the enemies of the Jews had not yet finished with him. On February 28th, 1944, a friend, having found out that an order for his arrest had come from Amsterdam to the Utrecht police, telephoned Cohen, who then, on good advice, moved to another friend's house (thus evading immediate arrest), and when night fell came to see Kruyt. Kruyt advised him strongly to "dive", and so give his many friends time to approach the German headquarters at the Hague. But this he refused to do, maintaining that he had done nothing wrong and that the whole affair must be due to some misunderstanding. Moreover, he refused Kruyt's advice to approach the S.S. headquarters at the Hague himself. Instead, he informed the Utrecht police of his whereabouts, was arrested and taken to Amsterdam, and on March 1st to Westerbork. Here further efforts were made by his friends to induce him to approach the Hague, but all in vain. The end was now not far off. All the evidence goes to show that on March 3rd he was transported (with many others) to the notorious "death" camp at Auschwitz and there murdered in a gas chamber. It is only fair to say that the good treatment Cohen received at the Hague was due to a certain Fräulein Slotke and her chief, Zöpf, who stood next in rank to Rauter. But towards the end of February 1944 Zöpf was not in Holland! So the enemies of Cohen seized their chance. As regards Cohen himself, Kruyt's opinion was that the shock of the earlier events had shaken his morale and enfeebled his judgment. It seems very probable that if he had taken Kruyt's good advice, his many friends would have safely hidden him until Zöpf returned to the Hague, and so saved his life.

So was murdered by some Nazi criminals the man who had worked in the friendliest co-operation with German men of science for fifty years, the man who had published a large proportion of his scientific work in the German language, the man who had organised the "Peace of Utrecht".

In conclusion, I express my sincere thanks to Professor H. R. Kruyt who kindly supplied me with a number of reports on the life and work of Ernst Cohen. I am also much indebted to Dr. S. Coffey and Mr. Francis Bolam for help with translations from the Dutch originals.

OBITUARY NOTICES.

HARRY THORNTON CALVERT.

1878—1947.

HARRY THORNTON CALVERT was born on May 3rd, 1878, in Leeds, Yorkshire, where he received his early education before proceeding to the Yorkshire College, now the University of Leeds, to study in the Honours School of Chemistry. Though only twenty years of age at the time of graduation in 1898, he had shown such promise as a student that he was at once awarded an 1851 Exhibition, and spent the next three years at the University of Leipzig, where he took the Ph.D. degree. His research at Leipzig was concerned with the dielectric properties of hydrogen peroxide.

After returning from Leipzig, Calvert was for a short time a demonstrator in chemistry under Professor Arthur Smithells at the University of Leeds. He then moved to Hull to serve as Chemist to Messrs. Reckitt & Sons, where he obtained valuable experience in chemistry applied to industry and an insight into industrial problems from many angles.

In 1903 he was appointed Chemist to the West Riding of Yorkshire Rivers Board, a joint committee of the Local Authorities of the area, which had been formed to administer the Rivers Pollution Prevention Acts. This change marked the beginning of his interest in the problems of water supply, sanitation, and prevention of river pollution. Calvert and Maclean Wilson, who was then Chief Inspector of the Rivers Board, proved to be ideal partners in guiding this important work. They were not inspectors in the narrow sense relying on legal authority: they studied in detail the problems with which the managers of local sewage works and industrial concerns were confronted in the disposal of waste liquids, and assisted in finding practicable methods of overcoming the difficulties, while at the same time having in mind the need to decrease the pollution of the local rivers, some of which were in a deplorable condition. It was after some years together on this work that Wilson and Calvert collaborated in writing the book "Trade Waste Waters—Their Nature and Disposal", which has long been accepted as the authoritative work on the subject. Calvert's outstanding investigations in this field were recognized in 1915 by the award of the degree of D.Sc. of the University of Leeds.

During the First World War, he was released on loan to the Department of Explosives Supply of the Ministry of Munitions. In his work in this Department, the wide knowledge he had acquired of a variety of chemical and other industries was of great value, and his success led to the award of the M.B.E.

In 1920 Calvert took up a new appointment as Chemical Inspector of the Ministry of Health, a post which gave him great scope for using his wide scientific and technical knowledge and his sound judgment. When the Water Pollution Research organization was established in 1927 under the Department of Scientific and Industrial Research he was the obvious choice as Director of Research, and he carried this responsibility while continuing his work for the Ministry of Health. With characteristic thoroughness, he steadily built up the work of the Water Pollution Research organization on a sure foundation. Every investigation, whether in the field of fundamental research in University Departments or in the nature of development work with large-scale installations in industrial establishments, was carefully planned before it was undertaken. Calvert was not interested in grandiose and costly schemes sketchily planned; and in consequence few research organizations can claim so much achievement in relation to the expenditure incurred as the Water Pollution Research organization. In all this work he had the full support of every member of the Research Board, for he had the power of inspiring interest and enthusiasm in all concerned, and in unobtrusively getting Boards, Committees, and staff working together amicably and efficiently.

On the outbreak of the Second World War in 1939 he was seconded to the Ministry of Supply as Deputy Controller of Sulphuric Acid, which post he retained until his retirement early in 1947 for reasons of health.

He will be remembered in his profession as an authority in the field of water supply and sanitation, not only in Great Britain, but throughout the world. Kind of heart and always ready to help, he made many close friends here, on the Continent, and in America.

In addition to his many scientific and technical papers and addresses in Great Britain, including chapters in the *Applied Chemistry Reports* and a Chadwick Public Lecture in 1926, Calvert was invited to give the Sedgwick Lecture in 1940 at the Massachusetts Institute of Technology, but owing to the war was unable to deliver the lecture. In 1944, he received the

Kenneth Allen award of the American Federation of Sewage Works Associations. He took a great interest in the Institute of Sewage Purification, of which he was President in 1927, 1928, and 1939. He was also a prominent Fellow of the Royal Sanitary Institute and of the Institution of Sanitary Engineers, a Professional Associate of the Institution of Water Engineers, and a member of the Society of Chemical Industry. He obtained the Associateship of the Institute of Chemistry in 1899 and the Fellowship in 1904, and had been a Fellow of the Chemical Society since April 22nd, 1903.

A. PARKER.

RICHARD CAYLEY GIFFARD MOGGRIDGE.

1915—1946.

RICHARD MOGGRIDGE was born on February 24th, 1915, and educated at Winchester and Balliol College, Oxford. After a short period of research in Oxford he worked until the outbreak of war with Professor Harington at University College Hospital Medical School. During the war he worked first at a Ministry of Supply Research Establishment, and later in other fields of scientific war research. At the end of the war he was appointed to the staff of Messrs. Courtaulds' Research Institute at Maidenhead, but his work there was cut short by his sudden death on March 26th, 1946, at the age of 31.

This bare statement conceals a career of considerable achievement and great promise. Richard Moggridge came to Balliol in 1933, holding both the Frazer Scholarship from Winchester and an open Domus Scholarship. He did not take much part in the social life of the College, but his work in chemistry showed from the very beginning a high standard of all-round achievement, and his essays (written in a minute but beautifully legible hand) were models of accuracy and exposition. His first piece of research was carried out with Dr. A. G. Ogston before he took his degree examination, and dealt with the electrometric titration of vitamin B₁ (*Biochem. J.*, 1935, 29, 866). However, his chief interest was in pure organic chemistry, and his fourth year was spent with Dr. S. G. P. Plant in investigating some structural problems in the indole series (*J.*, 1937, 1125).

He was placed near the top of the first class in his final examination, and left Oxford in 1937 to take up a research post in Professor C. R. Harington's laboratory in the University College Hospital Medical School. His interest in biochemical topics had been kindled by his first piece of research in Oxford, and his chief work in London was also concerned with vitamin B₁, as it dealt with the synthesis of an aminothiazolepropionic acid related to this vitamin. This rather difficult piece of synthetic work was successfully completed (*J.*, 1939, 443), and a later paper on the action of yeast on the synthetic amino-acid (*Biochem. J.*, 1940, 34, 685) is of considerable biochemical interest. As a side issue to this synthetic work Moggridge carried out some experiments in the glutamic acid series (*J.*, 1940, 706), and he also collaborated with Dr. Neuberger in a physico-chemical study of the hydrolysis of methylglucosaminides, which provided contributory evidence as to their structures (*J.*, 1938, 745).

During this period Richard Moggridge showed an increasing grasp of his subject, both in practical skill and in versatility of outlook, and everything pointed to a distinguished scientific career in the future. He was very popular with his colleagues, and happy both in his work and in his marriage to Daphne Simpson, which took place in 1938. When the war came he did not feel justified in continuing with his academic research work, and, after a short period as a full-time air raid warden, in April 1940 he took up a position in the Chemical Defence Research Establishment of the Ministry of Supply at Sutton Oak. His work there involved materials which were mostly unpleasant and often dangerous, but he devoted himself to it with unsparing energy, without regard for comfort or even health. Matters were aggravated by war-time accommodation difficulties, and it seems likely that the strain of this period contributed to his sudden death some years later. His work at Sutton Oak gave rise to a series of post-war publications on derivatives of 2 : 2'-dichlorodiethyl sulphide and related substances (*J.*, 1946, 813, 815, 816, 1105; 1947, 530).

In 1942 he was transferred to a different type of war job, which proved more congenial though no less strenuous. He was engaged on research and development work in connection with the supply of special equipment and arms to underground movements in enemy-occupied Europe. It was often necessary to improvise mines, weapons, explosive charges, special fuzes, and initiating mechanisms at very short notice, and Moggridge was given the responsibility of devising and carrying out such "user" trials as were practicable under these conditions. Risks

had to be taken, but by great thoroughness and attention to detail he succeeded in carrying out an arduous task with conspicuous success. During 1943—45 a constant stream of supplies was provided for various countries, and in France in particular the partisan movement was able to assist materially in the first few critical days after D-day.

In August 1945 Richard Moggridge became Senior Organic Chemist in the newly founded research station of Messrs. Courtaulds, Ltd., at Maidenhead. Here his previous interest in proteins and amino-acids fitted in with fundamental problems of textile research, and he had planned a programme of work for himself and his collaborators. However, he had barely had time to get this work under way when he died, suddenly and unexpectedly, in March 1946 just before his son Robin's third birthday.

Richard Moggridge was liked and respected by all his associates for his integrity of mind and character and his consideration for others. His scientific ability was matched by an interest in many things outside science which grew as he got older. His chief loves were music and climbing, in both of which he was joined by his wife. His knowledge of music was wide, but it was particularly choral music in which he took an active part, first at Winchester and in the Oxford Bach Choir, and later in London and Richmond. His climbing (in the Alps and the British hills) was also much more than a technical accomplishment, being based on a real love of mountain scenery and country people.

The last year of his life contained a new element, which he would certainly wish to be mentioned here. In June 1945 he and his wife joined a group of choral singers at St. Martin-in-the-Fields, and from that time the Christian faith became an increasingly important part of his life. It seems likely that, had he lived, he would have become even more intimately associated with the Church. On April 9th, 1946, his friends at St. Martin's held a choral service there in memory of him, and the beauty and sincerity of that occasion showed how deep an impression he had made among his fellow Christians. One phrase from that service forms a fitting conclusion to this notice: to know Richard was to realise "how possible it is to have at one's side goodness unaware of its good, greatness that honestly believes it is small".

My thanks are due to Dr. C. R. Harington and Professor D. M. Newitt for help in preparing this notice.

R. P. BELL.

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 3-(*m*-4-Xylidino)-4:5-benzocoumaran, 1047.
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FORMULA INDEX.

THE following index of organic compounds of known empirical formula is arranged according to Richter's system (see *Lexikon der Kohlenstoff-Verbindungen*).

The elements are given in the order, C, H, O, N, Cl, Br, I, F, S, P, and the remainder alphabetically.

The compounds are arranged—

Firstly, in groups according to the number of carbon atoms (thus C₁ group, C₂ group, etc.).

Secondly, according to the number of other elements besides carbon contained in the molecule (thus 5 IV indicates that the molecule contains five carbon atoms and four other elements).

Thirdly, according to the nature of the elements present in the molecule (given in the above order).

Fourthly, according to the number of atoms of each single element (except carbon) present in the molecule.

Salts are placed with the compounds from which they are derived. The chlorides, bromides, iodides, and cyanides of quaternary ammonium bases, however, are registered as group-substances.

C₁ Group.

CCl₄Se Perchloromethylselenol, 1083.

1 III

CH₄N₂S Thiourea, reaction of, with *s*-dichloroacetone, 323.

CH₃Cl₂Si Methylchlorosilane, 1593.

C₂ Group.

C₂H₂O₂ Oxalic acid, dihydrate, crystal and molecular structure of, 142; hydrated rare-earth salts of, 1687.

C₂H₄O₂ Glycollic acid, dithallium salt, 1381.

C₂H₆O Dimethyl ether, reaction of, with benzene, 928.

C₂H₆N₂ 2-Aminoethylamine, toluene-*p*-sulphonate, 502.

Ethylenediamine, bistoluene-*p*-sulphonate, 503.

C₂Cl₄Se Hexachlorodimethyl selenide, 1083.

2 III

C₂H₄Cl₂Sn Ethyltrichlorotin, 1450.

C₂H₅N₂S Methylammonium thiocyanate, 394.

C₂H₅Cl₂Si Ethyldichlorosilane, 1593.

2 IV

C₂HOCl₂S Trichlorothiolacetic acid, 141.

C₂H₂OCl₂S Dichlorothiolacetic acid, 140.

C₂H₄OCl₂Si₂ Ethylpentachlorodisiloxane, 1591.

C₂H₄O₂NS 2-Nitroethylthiol, 1480.

C₂H₄O₂NS 2-Nitroethanesulphonic acid, salts, 1483.

C₂H₄OCl₂Si₂ Dimethyltetrachlorodisiloxane, 1592.

C₃ Group.

C₃H₄O₂ Lactic acid, dithallium salt, 1381.

C₃H₆N₂ 1-Aminoethyl cyanide, hydrochloride, 1371.

Sarcosine nitrile, and its picrate, 661.

C₃H₁₀N₂ Trimethylenediamine, bistoluene-*p*-sulphonate, 503.

3 III

C₃H₃ON Oxazole, 102.

C₃H₄OCl₂ *s*-Dichloroacetone, reaction of, with thiourea, 323.

C₃H₄N₂S 2-Aminothiazole, chlorination of, with sulphuryl chloride, 431.

C₃H₈O₂TL Trithallium glycerol, 1381.

C₃H₆O₂S Methyl vinyl sulphone, 1515.

C₃H₈O₂TL Dithallium trimethylene glycol, 1382.

C₃H₇O₂N 1-Nitropropane, reaction of, with formaldehyde and ammonia, 924.

C₃H₇O₂N Methyl 2-nitroethyl ether, 1475.

C₃H₇Br₂Sn Allylpentabromostannic acid, 1450.

C₃H₈OS₂ 2:3-Dimercaptopropanol, 594.

C₃H₇O₂N₂ 2-Nitroisopropylamine, hydrochloride, 1488.

C₃H₇ON Methyl 2-aminoethyl ether, picrate, 1476, 1477.

C₃H₈NS₂ 2:3-Dimercaptopropylamine, 594.

3 IV

C₃H₄ON₂S 2-Thiohydantoin, 580.

C₃H₇O₂NS Methyl 2-nitroethyl sulphide, 1479.

2-Nitropropylthiol, 1481.

C₃H₇O₂NS Methyl 2-nitroethyl sulphone, 1479.

C₃H₇O₂NS 1- and 2-Nitropropane-2-sulphonic acids, salts, 1483.

C₃H₇ON₂Cl α -Amidinoacetamide, hydrochloride, 617.

C₃H₇O₂NS Methyl 2-aminoethyl sulphone, 1479.

C₄ Group.

C₈H₁₈, *iso*Butylene, dimerisation of, 250.

4 II

- C₆H₈O₄, Acetylenedicarboxylic acid, dihydrate, crystal and molecular structure of, 148.
 C₆H₈O₄, *meso*Tartaric acid, tetrathallium salt, 1380.
 C₆H₈O₄, Vinyl acetate, vapour, polymerisation of, 1201, 1211.
 C₆H₈O₄, α -Methoxyacrylic acid, 1033.
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 C₆H₈N₂, 3-Amino-*n*-propyl cyanide, and its hydrochloride, 1370.
 C₆H₁₀N₂, *NN'*-Dimethylacetamidine, salts, 385.
 C₆H₁₂N₂, Tetramethylenediamine, bistoluene-*p*-sulphonate, 503.

4 III

- C₆H₈O₂N Oxazole-4-carboxylic acid, 102.
 C₆H₈ON 2-Methyloxazole, and its picrate, 101.
 C₆H₈O₂N₂, 2-Nitropropyl cyanides, 1501.
 C₆H₈O₂TI₄, Tetrathallium erythritol, 1381.
 C₆H₈N₂S₂, 2-Amino-4-mercaptomethylthiazole, 324.
 5-Amino-2-mercapto-4-methylthiazole, hydrochloride, 1607.
 C₆H₈O₂N 2-Nitrobut-2-ene, 1477.
 C₆H₈Cl₂S₂, 2,2'-Dichlorodiethyl sulphide, thermal decomposition of, 318.
 C₆H₈O₂N 2-Acetoxyethylamine, and its hydrochloride, 530.
 C₆H₈O₂N Methyl 2-nitropropyl ethers, 1476.
 Nitro-*tert.*-butyl alcohol, 1518.
 C₆H₈O₂N 2-Nitro-3-methoxy-*n*-propyl alcohol, 1476.
 C₆H₁₀ON₂, β -Amino*iso*butyramide, picrate, 1502.
 C₆H₁₀OS₂, Methyl 2:3-dimercaptopropyl ether, 594.
 C₆H₁₀O₂N₂, 2-Nitro-3-aminobutane, hydrochloride, 1488.
 1-Nitro-2-amino-2-methylpropane, hydrochloride, 1488.
 C₆H₁₁ON Butoxyamine, hydrobromide, 968.
 Methyl-2-methoxyethylamine, and its picrolonate, 313.
 C₆H₁₁NS₂, 2:2'-Dimercaptodiethylamine, and its hydrochloride, 322.
 C₆H₁₁ClSi Diethylchlorosilane, 1593.
 C₆OCl₄Si₂ Bispentachloroethyltetrachlorodisiloxane, 1592.

4 IV

- C₆H₈ClSAs 2-(2-Chlorovinyl)-1:3-dithia-2-arsacyclopentane, 595.
 C₆H₈O₂NS 2-Nitroethyl thiolacetate, 1480.
 C₆H₈O₂NS Carboxymethyl 2-nitroethyl sulphide, 1480.
 C₆H₈O₂NS Carboxymethyl 2-nitroethyl sulphone, 1480.
 C₆H₈O₂NCl 3-Chloropropyl carbamate, 179.
 C₆H₈O₂N₂S Di-(2-nitroethyl) sulphide, 1480.
 C₆H₈O₂N₂S Di-(2-nitroethyl) sulphone, 1480.
 C₆H₈OSAs 2-Methyl-4-hydroxymethyl-1:3-dithia-2-arsacyclopentane, 595.
 C₆H₈O₂NS Carboxymethyl 2-aminoethyl sulphide, 1480.
 Methyl 2-nitropropyl sulphide, 1479.
 Nitro-*tert.*-butylthiol, 1480.
 C₆H₈O₂NS Methyl 2-nitropropyl sulphone, 1479.
 C₆H₈O₂NS 2-Nitrobutane-3-sulphonic acid, salts, 1484.
 1-Nitro-2-methylpropane-2-sulphonic acid, sodium salt, 1483.
 C₆H₁₀ONCl Formimido*iso*propyl ethyl hydrochloride, 101.
 C₆H₁₀OClSi₂ Diethyltetrachlorodisiloxane, 1591.
 C₆H₁₀O₂NCl 2-Chloroethyl *N*-dimethylcarbamate, 179.
 C₆H₁₁O₂NS 2-Aminobutane-3-sulphonic acid, 1484.
 1-Amino-2-methylpropane-2-sulphonic acid, 1484.

C₅ Group.

- C₈H₁₀O₂, But-1-en-3-yne-1-carboxylic acid, and its *S*-benzylisothiuronium salt, 1589.
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 C₈H₈N₂, 2-Aminopyridine, toluene-*p*-sulphonate, 387.
 N-Aminopyridine, salts, 65.
 C₈H₈N₂, 3-Amino-6-methylpyridazine, and its salts, 243.
 C₈H₁₀O₄, 3-Deoxy-*L*-xylose, 972.
 C₈H₁₀N₂, Amino-*tert.*-butyl cyanide, and its salts, 1502.
 2-Amino-1-methyl-*n*-propyl cyanide, hydrochloride, 1502.
 C₈H₁₁N Piperidine, benzenesulphonate, 385.
 C₈H₁₁N, 1:3-Diamino-2:2-dimethylpropane, 1502.

5 III

- C₈H₈O₂N₂, 5-Nitroso-4:6-dihydroxy-2-isonitrosomethylpyrimidine, and its sodium salt, 947.
 C₈H₈N₂Cl₂, 4:6-Dichloro-5-methylpyrimidine, 50.
 C₈H₈ON 3-Hydroxypyridine, methiodide, 188.
 C₈H₈ON, 5:6-(4:5-Triazolo)-4-hydroxy-2-methylpyrimidine, and its sodium hydrogen salt, 947.
 C₈H₈O₂N 2-Methyloxazole-4-carboxylic acid, 101.
 C₈H₈N₂Cl 3-Chloro-6-methylpyridazine, and its salts, 242.
 C₈H₈N₂Cl₂, 2:6-Dichloro-4-guanidinopyrimidine, 733.
 C₈H₈ON, 6-Methyl-3-pyridazone, and its salts, 241, 242.
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- $C_4H_6O_2N_2$ 4:6-Dihydroxy-5-methylpyrimidine, 49.
 $C_4H_5N_2Cl$ 4-Chloro-2-amino-5-methylpyrimidine, 45.
 4-Chloro-6-amino-5-methylpyrimidine, 50.
 $C_4H_5O_2N$ 2-Nitro-3-methylbuta-1:3-diene, 1474.
 3-Nitropenta-1:3-diene, 1473.
 $C_4H_6O_2N_2$ 2-Methylamino-4:6-dihydroxypyrimidine, 732.
 4-Methylamino-2:6-dihydroxypyrimidine, 732.
 $C_4H_5O_2N_2$ 4-Guanidino-2:6-dihydroxypyrimidine, 733.
 $C_4H_5O_2N_2$ 1-Nitro-5:5'-dimethylhydantoin, 334.
 $C_4H_5O_2N_2$ Nitro-*tert.*-butyl cyanide, 1502.
 2-Nitro-1-methyl-*n*-propyl cyanide, 1502.
 $C_4H_5O_2N$ 5-Amino-4:6-dihydroxy-2-aminomethylpyrimidine, and its hydrochloride, 947.
 $C_4H_5O_2Cl_2$ 4-Chlorobutyl chloroformate, 178.
 $C_4H_5O_2S$ β -Acetylthiopropaldehyde, 1610.
 $C_4H_5N_2S$ 4-Methyl-2-aminomethylthiazole, 1373.
 $C_4H_5N_2S$ 5:5-Dimethyl-2:4-dithiohydantoin, 683.
 $C_4H_5N_2S$ 2-Amino-4-thiazolylmethylisothiourea, and its dihydrochloride, 324.
 2:2'-Diamino-4:4'-spirothiazoline, and its salts, 325.
 $C_4H_5O_2N$ 1-Methoxycyclopropane-1-carboxamide, 1034.
 $C_4H_5O_2N$ 2-Nitro-1-hydroxy-3-methylbut-3-ene, 1474.
 $C_4H_5N_2S$ 4-Imino-5:5-dimethyl-2-thiohydantoin, 685.
 C_4H_5ClS 2-Methyl-4-chloromethyl-1:3-dithiolan, 594.
 $C_4H_{10}ON_2$ 1:3-Dimethyliminazolid-2-one, 315.
 $C_4H_{10}OS_2$ 2-Methyl-4-hydroxymethyl-1:3-dithiolan, 594.
 $C_4H_{10}O_2N$ 1:3-Dinitro-2:2-dimethylpropane, 1518.
 $C_4H_{10}N_2S$ α -Amino- γ -methylthio-*n*-butyronitrile, oxalate, 1611.
 $C_4H_{10}N_2S$ 4-Hydrazino-5:5-dimethyl-2-thiohydantoin, 686.
 $C_4H_{11}O_2N$ 2-Nitropentane, 1499.
 Nitro-neopentane, 1498.
 $C_4H_{11}O_2N$ Methyl nitro-*tert.*-butyl ether, 1476.
 2-Nitro-3-methoxybutane, 1476.
 1- and 3-Nitro-2-methylbutan-2-ols, 1519.
 Propyl 2-nitroethyl ethers, 1476.
 $C_4H_{11}O_2N$ 2-Nitro-2'-methoxydiethyl ether, 1476.
 $C_4H_{11}O_2N$ 2-Nitro-2-methoxymethylpropane-1:3-diol, 1477.
 $C_4H_{11}NCl_2$ Methyl-di-(2-chloroethyl)amine, and its salts, 516.
 $C_4H_{11}ON_2$ β -Amino- $\alpha\alpha$ -dimethylpropionamide, and its salts, 1502.
 β -Amino- α -methylbutyramide, picrolonate, 1502.
 $C_4H_{12}O_2N_2$ 2-Nitro-2-hydroxymethylbutylamine, and its hydrochloride, 928.
 $C_4H_{12}ON_2$ 2-Amino-3-methoxybutane, and its platinichloride, 1477.
 3-Amino-2-methylbutan-2-ol, 1519.
 Ethyl-2-methoxyethylamine, and its picrolonate, 313.
 2-*iso*Propoxyethylamine, and its picrolonate, 313.
 $C_4H_{13}O_2N$ Methyl-di-(2-hydroxyethyl)amine, and its di-*p*-nitrobenzoate, 516.
 Methyl-2-(2-hydroxyethoxy)ethylamine, and its salts, 532.
 $C_4H_{13}O_2N$ 2-Amino-2-methoxymethylpropane-1:3-diol, picrolonate, 1477.
 $C_4H_{13}O_2P$ Diethyl methylphosphonate, 1466.
 $C_4H_{13}NCl_2$ β -Chloroethylisopropylamine hydrochloride, 59.
 Dimethyl- β -chloropropylamine hydrochloride, 59.
 $C_4H_{13}NS_2$ Methyl-2:2'-dimercaptodiethylamine, and its salts, 321.
 $C_4H_{13}IS_2$ Dimethyl-2-methylthioethylsulphonium iodide, 770.
 $C_4H_{13}ON_2$ 5-Amino-2-methylpyrrolidine *N*-oxide, 1511.
 $C_4H_{13}O_2N_2$ 4-Amino-*N*- β -diethylaminoethylphenol *N*-methylurethane, salts, 190.

5 IV

- $C_5H_8N_2ClBr$ 4-Chloro-5-bromo-2-amino-6-methylpyrimidine, 46.
 $C_5H_7O_2ClS$ α -Chloro- β -(acetylthio)propionic acid, 1033.
 $C_5H_7O_2BrS$ α -Bromo- β -(acetylthio)propionic acid, 1033.
 C_5H_7ONBr α -Bromo- $\beta\beta$ -dimethylacrylamide, 1033.
 C_5H_7ONCl Morpholine-*N*-carboxychloride, 313.
 $C_5H_8ClS_2As$ 2-(2-Chlorovinyl)-1:3-dithia-2-arsacyclohexane, 595.
 4-Methyl-2-(2-chlorovinyl)-1:3-dithia-2-arsacyclopentane, 595.
 $C_5H_{10}O_2NCl$ 4-Chlorobutyl carbamate, 179.
 $C_5H_{11}O_2NS$ Methyl 2-nitro-1-methylpropyl sulphide, 1479.
 $C_5H_{11}O_2N_2Cl$ 2-Keto-4:4-dimethyl-2:3:5:6-tetrahydro-1:3:4-oxadiazinium chloride, 181.
 $C_5H_{11}ONCl$ Methyl-2-chloroethyl-2-hydroxyethylamine, and its salts, 519.
 $C_5H_{13}O_2N_2Cl$ 2-Dimethylaminoethanol hydrochloride urethane, 181.

5 V

- $C_5H_7OCIS_2As$ 5-Hydroxy-2-(2-chlorovinyl)-1:3-dithia-2-arsacyclohexane, 595.
 4-Hydroxymethyl-2-(2-chlorovinyl)-1:3-dithia-2-arsacyclopentane, 595.
 $C_5H_{14}O_2NClS$ Methyl 2-dimethylaminoethanesulphonate hydrochloride, 181.

 C_6 Group.

- C_6H_6 Benzene, reaction of, with methyl ether, 928.

6 II

- $C_6H_8O_4$ Diacetylenedicarboxylic acid, dihydrate, crystal structure of, 1145.
 $C_6H_8O_4$ Methylbut-1-en-3-yne-1-carboxylate, 1589.

- $C_5H_8O_5$ Pent-3-en-1-yn-5-ol-1-carboxylic acid, and its *S*-benzylisothiuronium salt, 1588.
 $C_6H_{10}O_5$ Hex-2-en-4-yne-1:6-diol, 1589.
 $C_6H_{10}O_4$ 2:3-Anhydro- α -methyl-*L*-ribose, 972.
 $C_6H_{10}O_4$ 2:3-Anhydro- β -methyl-*L*-ribose, 971.
 $C_6H_{10}O_4$ 1:4:3:6-Dianhydro-*L*-iditol, hemihydrate, 1404.
 $C_6H_{10}O_5$ 3-Methyl 1-arabofuranolactone, 1063.
 $C_6H_{10}O_5$ Mucic acid, thallous salt, 1381.
 $C_6H_{10}O_5$ Saccharic acid, thallium hydrogen salt, 1381.
 $C_6H_{10}N_4$ 2:5-Diamino-4:6-dimethylpyrimidine, 51.
 $C_6H_{10}S$ *cyclo*Hexene thioepoxide, 1530.
 $C_6H_{12}O_4$ 3-Deoxy- β -methyl-*L*-xylopyranoside, 971.
 $C_6H_{12}O_5$ 2-Methyl *D*-arabinose, 1343.
 $C_6H_{12}O_5$ 3-Methyl arabinose, 1063.
 $C_6H_{12}N_2$ 5-Aminoamyl cyanide, 1370.
 $C_6H_{12}N_2$ 5-Imino-2:2-dimethylpyrrolidine, and its picrate, 1510.
 $C_6H_{12}S$ Propyl allyl sulphide, 1529.
 $C_6H_{12}N$ 2:2-Dimethylpyrrolidine, and its picrate, 1510.
 $C_6H_{12}N$ 2-Amino-3-methylpentane, 1497.
 $C_6H_{12}N_2$ 2:4-Diamino-2-methylpentane, 1398.
 $C_6H_{12}N_2$ Hexamethylenediamine, bistoluene-*p*-sulphonate, 503.

6 III

- $C_6H_7ON_2$ 2-Hydroxy-5-cyanopyridine, 88.
 $C_6H_7O_2N_2$ *p*-Dinitrobenzene, crystal structure of, 884.
 $C_6H_7O_2N_2$ *iso*Nicotinic acid, picrate, 1630.
 $C_6H_7O_2Br$ 2-Bromoacetyl furan, 1658.
 $C_6H_7O_2Ti$ Hexathallium inositol, 1382.
 $C_6H_7N_2Cl_2$ 2:5-Dichloro-3:6-dimethylpyrazine, 1182.
 $C_6H_7Cl_2Si$ Phenyldichlorosilane, 1593.
 C_6H_7ON 3-Hydroxy-2-methylpyridine, and its picrate, 133.
 $C_6H_7O_2N$ Ethyl oxazole-4-carboxylate, 102.
 $C_6H_7N_2Cl$ 2-Chloro-3:6-dimethylpyrazine, 1182.
 $C_6H_7N_2Cl_2$ 2:6-Dichloro-4-dimethylaminopyrimidine, 732.
 $C_6H_7N_2Cl_2$ 4:6-Dichloro-2-dimethylaminopyrimidine, 732.
 C_6H_7ON 2:5-Dimethylpyrazine *N*-oxide, 1184.
 C_6H_7ON 2-Hydroxy-3:6-dimethylpyrazine, and its picrate, 372.
 C_6H_7ON 3-Methoxy-6-methylpyridazine, and its hydrochloride, 243.
 $C_6H_7O_2N_2$ 5-Amidinofurfuryl alcohol hydrochloride, and its salts, 398.
 $C_6H_7O_2N_2$ 2:5-Dimethylpyrazine di-*N*-oxide, 1184.
 $C_6H_7O_2N_2$ 2-Dimethylamino-4:6-dihydroxypyrimidine, 733.
 $C_6H_7O_2N_2$ 4-Dimethylamino-2:6-dihydroxypyrimidine, 732.
 $C_6H_7O_2Br$ Methyl α -bromo- $\beta\beta$ -dimethylacrylate, 1033.
 $C_6H_7N_2S$ 4-Amino-2-methylthio-6-methylpyrimidine, 49.
 $C_6H_7O_2Cl_2$ 5-Chloropentyl chloroformate, 178.
 $C_6H_7O_2S$ β -Acetylthio-*n*-butaldehyde, 1610.
 $C_6H_7O_2N_2S$ 4-Methyl-2-(1'-aminoethyl)thiazole, 1375.
 $C_6H_7O_2N_2S$ 4-Methyl-2-(2'-aminoethyl)thiazole, 1376.
 $C_6H_7O_2N_2S$ 5-Methyl-5-ethyl-2:4-dithiohydantoin, 683.
 $C_6H_7O_2N_2S$ 5- β -Methylthioethylthiohydantoin, 1612.
 C_6H_7ON 2:2-Dimethyl-5-pyrrolidone, and its hydrochloride, 1511.
 C_6H_7OCl 1-Chloro-3-methylpentan-2-one, 375.
 $C_6H_7O_2N$ 2-Nitro-4-methylpent-2-ene, 1484.
 $C_6H_7O_2N$ α -Ethoxyethylideneaminoacetic acid, potassium salt, 100.
 $C_6H_7O_2N$ Nitro-*tert*-butyl acetate, 1518.
 $C_6H_7O_2N$ 2-Nitro-1-hydroxy-3-methyl-2-hydroxymethylbut-3-ene, 1473.
 $C_6H_7O_2Br$ 3-Bromoglucose, 17.
 C_6H_7ClS 2:2-Dimethyl-4-chloromethyl-1:3-dithiolan, 595.
 C_6H_7ON 5-Amino-2:2-dimethylpyrrolidine, *N*-oxide, and its salts, 1510.
 C_6H_7ON 1:3-Dimethylhexahydropyrimid-2-one, 315.
 C_6H_7OS 2:2-Dimethyl-4-hydroxymethyl-1:3-dithiolan, 595.
 $C_6H_7O_2S$ Butyl vinyl sulphones, 1515.
 $C_6H_7O_2N_2$ 5-Nitro-5-ethyltetrahydro-1:3-oxazine, and its salts, 927.
 $C_6H_7O_2N_2$ 1:3-Dinitro-2:2-dimethylbutane, 1519.
 $C_6H_7O_2N_2$ Dinitromethylpentanes, 1491.
 $C_6H_7N_2S$ α -Amino- γ -ethylthio-*n*-butyronitrile, oxalate, 1612.
 C_6H_7ON 1-Amino-3-methylpentan-2-one, hydrochloride, 375.
 $C_6H_7O_2N$ Methyl β -amino- $\alpha\alpha$ -dimethylpropionate, and its hydrochloride, 1503.
 $C_6H_7O_2N$ 1-Nitro-2:2-dimethylbutane, 1497.
 $C_6H_7O_2N$ 2-Nitro-3-methylpentane, 1497.
 $C_6H_7O_2N$ *n*-Butyl 2-nitroethyl ether, 1476.
 $C_6H_7O_2N$ Ethyl nitro-*tert*-butyl ether, 1476.
 $C_6H_7O_2Cl$ Methyl-2-hydroxyethyl-2-[2-(2-hydroxyethoxy)ethoxy]ethylamine, and its salts, 531.
 $C_6H_7O_2P$ Diethyl vinylphosphonate, 1467.
 $C_6H_7O_2N$ 2-Nitro-3-methoxy-2-methyl-*n*-butyl alcohol, 1477.
 $C_6H_7O_2N_2$ Di-(2-nitroisopropyl)amine, 1488.
 $C_6H_7O_2N$ 2-Methyl 1-arabonamide, 1225.
 $C_6H_7O_2N$ 3-Methyl 1-arabonamide, 1064.
 $C_6H_7NCl_2$ Ethyldi-(2-chloroethyl)amine, and its salts, 516.
 C_6H_7ClS 2-Chloroethyl *isobutyl* sulphide, 1515.

- $C_6H_{11}O_2N_2$ Diethyl-2-nitroethylamine, salts, 1488.
 $C_6H_{11}O_2N_2$ Diglycylethylenediamine, 129.
 $C_6H_{11}ON_2Cl$ Dimethylethyl- β -chloroethylammonium hydroxide, picrate, 59.
 $C_6H_{11}ON_2$ 2-*n*-Butoxyethylamine, and its picrolonate, 313.
 Dimethylethyl- β -hydroxyethylammonium hydroxide, picrate, 59.
 Ethyl-2-ethoxyethylamine, and its picrolonate, 313.
 Hexoxyamine, and its salts, 966.
 $C_6H_{11}ON_2$ Butoxydiguanide, nitrate, 966.
 $C_6H_{11}NCl_2$ Dimethylethyl- β -chloroethylammonium chloride, 59.
 $C_6H_{11}NS_2$ 2:2'-Dimercaptotriethylamine, and its salts, 322.
 $C_6H_{11}NS_2$ 2:2':2''-Trimercaptotriethylamine, and its salts, 322.
 $C_6H_{11}O_2N_2$ 1:6-Hexamethylenedioxyamine, salts, 967.
 $C_6H_{11}O_2Si$ Diethyldimethoxysilane, 1594.

6 IV

- $C_6H_4O_2N_2Cl_2$ 2:6-Dichloro-4-nitroaniline, deamination of, 734.
 $C_6H_4ON_2S$ 6-Hydroxy-8-mercapto-2-methylpurine, 946.
 $C_6H_4ON_2S$ 2-Chloro-5-hydroxy-3:6-dimethylpyrazine, 1182.
 4-Chloro-6-hydroxy-2:5-dimethylpyrimidine, 1358.
 $C_6H_4ON_2S$ 1-Nitro-2-(2-furyl)ethanesulphonic acid, sodium salt, 1484.
 $C_6H_4O_2N_2S$ 5-Amino-4-carbethoxythiazole, 1598.
 2-Amino-4-methylthiazole-5-acetic acid, and its hydrochloride, 591.
 4-Methyl-2-aminomethylthiazole-5-carboxylic acid, 1374.
 $C_6H_4O_2N_2S_2$ 5-Amino-2-mercapto-4-carbethoxythiazole, 1607.
 $C_6H_4O_2NS$ 1-Amino-2-(2-furyl)ethanesulphonic acid, 1484.
 $C_6H_{10}O_2N_2Br_2$ 2:4-Dibromonitro-3-methylpentane, 1491.
 $C_6H_{11}O_2N_2Br$ 2-Bromonitro-4-nitro-2-methylpentane, 1491.
 $C_6H_{11}O_2NS$ Carbethoxymethyl 2-nitroethyl sulphone, 1480.
 $C_6H_{11}O_2NCl$ 2-Chloroethyl *N*-propylcarbamate, 179.
 5-Chloropentyl carbamate, 179.
 $C_6H_{11}O_2NS$ *S-n*-Propylcysteine, 428.
 $C_6H_{11}O_2NCl$ 2-Chloroethyl *N*-diethylcarbamate, 179.
 2-Chloroethyl-di-(2-hydroxyethyl)amine, salts, 529.
 $C_6H_{11}O_2BrP$ Diethyl bromoethylphosphonate, 1467.
 $C_6H_{11}OCl_2Si_2$ Triethyltrichlorodisiloxane, 1591.
 $C_6H_{11}O_2NS$ 2-Amino-4-methylpentane-3-sulphonic acid, 1484.

6 V

- $C_6H_4O_2NCl_2As$ *p*-Nitrophenyldichloroarsine, 667.
 $C_6H_{11}OCIS_2As$ 4-Methoxymethyl-2-(2-chlorovinyl)-1:3-dithia-2-arsacyclopentane, 595.
 $C_6H_{11}O_2NCIS$ α -Amino- γ -mercapto- γ -methyl-*n*-valeric acid, 1612.
 $C_6H_{11}ON_2CIS$ 2-Dimethylaminoethanol hydrochloride *N*-methylthiourethane, 181.

C₇ Group.

- C_7H_8 Toluene, nitration of, 921.
 C_7H_{10} 2:5-Dihydrotoluene, 1647.

7 II

- $C_7H_8O_2$ 3-Hydroxy-4-methylpent-4-en-1-yne-1-carboxylic acid, 806.
 $C_7H_8N_2$ Benzamidine, picrate, 392.
 C_7H_8N 2:3-Dimethylpyridine, methiodide, 1698.
 $C_7H_{10}O$ 2:3-Dihydroanisole, 1646.
 $C_7H_{11}N_2$ 4:6-Dimethyl-2-aminomethylpyrimidine, and its hydrochloride, 1374.
 $C_7H_{12}O$ Δ^1 -cycloHexene methyl ether, 105.
 $C_7H_{12}O_2$ 2:3-Dihydroxy-[2:2:1]bicycloheptane, 819.
 $C_7H_{12}O_2$ β -tert.-Butoxyacrylic acid, 1033.
 $C_7H_{13}N$ cycloHexylmethylenimine, 1116.
 $C_7H_{11}O_2$ 2-Methyl β -methyl-D-arabopyranoside, 1343.
 2-Methyl β -methyl-L-arabopyranoside, 1343.
 $C_7H_{11}N_2$ 2-*n*-Butyldihydroglyoxaline, and its salts, 500.
 $C_7H_{11}S$ 1-Methylcyclohexane-2-thiol, 1537.
 2-Methylcyclohexanethiol, 138.
 $C_7H_{11}N_2$ α -Ethyl- α -isopropylacetamidine, and its hydrochloride, 741.
 4:4:6-Trimethylhexahydropyrimidine, 1398.
 $C_7H_{13}N_2$ 2-Amino-1-diethylaminopropane, 1513.
 2:4-Diamino-2:3-dimethylpentane, picrate, 1491.
 γ -Diethylaminopropylamine, salts, 947.
 $C_7H_{20}N_4$ β -Diethylaminoethylguanidine, dihydriodide, 52.

7 III

- $C_7H_8N_2Cl$ *p*-Chlorophenylcyanamide, 947.
 $C_7H_8O_2N_2$ 2:4-Dinitrotoluene, kinetics of nitration of, 474.
 $C_7H_8O_2N$ 3-Hydroxy-6-methylpicolinic acid, 133.
 $C_7H_8N_2Br$ *p*-Bromobenzamidine, salts, 392, 393.
 $C_7H_8N_2S$ 2-Amino-4-(2'-pyrryl)thiazole, 1659.
 $C_7H_8ON_2$ *N*-Acetamidopyridine, hydrochloride, 66.
 Benzamidoxime, hydrobromide, 969.
 p -Hydroxybenzamidine, and its salts, 392, 393.
 $C_7H_8N_2Cl_2$ 4:6-Dichloro-2-methyl-5-ethylpyrimidine, 1360.

- C₈H₈N₂S** 2:4-Dimethyl-5-cyanomethylthiazole, and its picrate, 1402.
C₈H₈ON 3-Acetamide-6-methylpyridazine, and its salts, 243.
C₈H₈O₂N 5-Hydroxy-2-methyl-6-hydroxymethylpyridine, and its salts, 133.
 3-Hydroxy-4-methylpent-4-en-1-yne-1-carboxamide, 807.
C₈H₈O₂N₂ 5-Formamido-4-hydroxy-2:6-dimethylpyrimidine, 50.
 3-Nitro-1:5-dicyanopentane, 1507.
C₈H₈O₂N Ethyl 2-methyloxazole-4-carboxylate, 101.
C₈H₈O₂N *p*-Nitro-*o*-methoxyphenylhydrazine, 465.
C₈H₈N₂Cl 4-Chloro-*m*-tolylhydrazine, 1559.
C₈H₁₀ON 2-Hydroxy-3:5:6-trimethylpyrazine, 376.
C₈H₁₀N₂S 5:5-*cyclo*Tetramethylene-2:4-dithiohydantoin, 683.
C₈H₁₁O₂N 2-Nitro-1-acetoxy-3-methylbut-3-ene, 1474.
C₈H₁₁N₂S 4-Amino-2-methylthio-5:6-dimethylpyrimidine, 48.
C₈H₁₁N₂S₂ Methyl-2:2'-dithiocyanodietethylamine, hydrochloride, 322.
C₈H₁₁O₂N₂ 3-Nitro-1:2-dimethyl-*n*-butyl cyanide, 1507.
C₈H₁₂O₂Cl 6-Chlorohexyl chloroformate, 178.
C₈H₁₂N₂S 4-Methyl-2-(3'-aminopropyl)thiazole, 1377.
C₈H₁₂N₂S₂ 5:5-Diethyl-2:4-dithiohydantoin, 683.
 5-Methyl-5-*n*-propyl-2:4-dithiohydantoin, 683.
 5-Methyl-5-*isopropyl*-2:4-dithiohydantoin, 683.
C₈H₁₂N₂S₂ 5-β-Ethylthioethylthiohydantoin, 1612.
C₈H₁₃ON 1:2:2-Trimethyl-5-pyrrolidone, 1511.
C₈H₁₃O₂N 1-Nitro-2:2-dimethylpent-4-ene, 1498.
C₈H₁₃O₂Cl 2-Chloro *α*-methylaltroside, 14.
 3-Chloro *α*-methylglucoside, 14.
C₈H₁₃O₂Br 2-Bromo *α*-methylaltroside, 16.
 3-Bromo *α*-methylglucoside, 16.
C₈H₁₄ON *N*-Acetamidopiperidine, hydrochloride, 66.
 1:3-Diethyliminazolid-2-one, 315.
 2-Keto-4:4:6-trimethylhexahydropyrimidine, 1398.
C₈H₁₄O₂N₂ Methyl 2-nitro-1:2-dimethylpropyl ketoxime, 1491.
C₈H₁₄O₂N₂ 2:4-Dinitro-2:3-dimethylpentane, 1490.
C₈H₁₄O₂S 3-Methylthio β-methyl-*L*-xylopyranoside, 971.
C₈H₁₄O₂N₂ Methyl 2:4-dinitro-2-methylamyl ether, 1491.
C₈H₁₄O₂N Ethyl β-amino-*αα*-dimethylpropionate, hydrochloride, 1503.
C₈H₁₄O₂N *n*-Amyl 2-nitroethyl ether, 1476.
 Methyl-2-hydroxyethyl-2-acetoxyethylamine, 517.
 2-Nitroisopropyl *n*-butyl ether, 1476.
C₈H₁₄O₂P Diethyl propenylphosphonate, 1467.
C₈H₁₄O₂N Substance, and its hydrochloride, from hydrolysis of 3-amino 4:6-benzylidene *α*-methylaltrosic, 21.
C₈H₁₄NCl₂ Di-(2-chloroethyl)-*n*- and -*iso*-propylamines, and their salts, 516.
 Methyl-di-(2-hydroxy-*n*-propyl)amine, and its picrate, 517.
C₈H₁₄ON₂ 3-Ureidoheptane, 1496.
C₈H₁₄O₂N₂ 2-Nitro-1-diethylaminopropane, 1513.
C₈H₁₅ON *O*-Heptoxyamine, and its hydrobromide, 966.
C₈H₁₅ON₂ Hexoxyguanidine, nitrate, 966.
C₈H₁₅O₂N Di-(2-hydroxyethyl)*isopropyl*amine, and its salts, 516.
 Methyl-di-(2-hydroxy-*n*-propyl)amine, and its picrate, 517.
C₈H₁₅O₂N Methyl-2-hydroxyethyl-2-(2-hydroxyethoxy)ethylamine, and its salts, 517, 531.
C₈H₁₅O₂P Diisopropyl methylphosphonate, 1466.
C₈H₁₅NS₂ 2-Aminopropaldehyde diethylmercaptal, and its picrate, 372.
C₈H₁₅N₂S₂ Methyl-di-(2-isothioureido-*S*-ethyl)amine, trihydrochloride, 321.
C₈H₁₆ON₂ Methyl 2:4-diamino-2-methylamyl ether, 1492.

7 IV

- C₈H₈NCl₂Sb** *p*-Cyanophenylstibinous chloride, 7.
C₈H₈NI₂Sb *p*-Cyanophenylstibinous iodide, 8.
C₈H₈ON₂S 2-Amino-4-(2'-furyl)thiazole, 1658.
C₈H₈ONS 4-Nitrosothioanisole, 852.
C₈H₈N₂ClS 6-Chloro-8-methylthio-2-methylpurine, 947.
C₈H₈ONBr 5-Hydroxy-2-methyl-6-bromomethylpyridine, hydrobromide, 133.
C₈H₈ON₂Cl 4-Chloro-5-formamido-2:6-dimethylpyrimidine, 50.
C₈H₈ON₂S 6-Hydroxy-8-methylthio-2-methylpurine, 946.
C₈H₈ONS 4-Hydroxyaminothioanisole, 851.
C₈H₈ON₂Cl 4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine, 1360.
C₈H₈O₂NS 2:4-Dimethylthiazole-5-acetic acid, and its hydrobromide, 1402.
 4-Ethylsulphonylpyridine, 53.
C₈H₈N₂ClS 4-Chloro-2-methylthio-5:6-dimethylpyrimidine, 47.
C₈H₁₀ON₂S 2:4-Dimethylthiazole-5-acetamide, and its picrate, 1402.
C₈H₁₀O₂N₂S 5-Amino-2-methylthio-4-carbethoxythiazole, and its hydriodide, 1608.
C₈H₁₀O₂N₂S *m*-Aminobenzenesulphonamidoguanidine, 822.
C₈H₁₀NCIS 1-Chloro-2-thiocyanocyclohexane, 1529.
C₈H₁₀NIS 4-Ethylthiopyridine hydriodide, 53.
C₈H₁₀ONBr 2-(2-Bromopropionamido)butan-3-one, 376.
C₈H₁₀ON₂S 4-2'-Hydroxyethylimino-5:5-dimethyl-2-thiohydantoin, 686.
C₈H₁₀O₂N₂S *N*-Thiocarbethoxymorpholine, 1598.
C₈H₁₀O₂N₂Br 2-Bromonitro-4-nitro-2:3-dimethylpentane, 1490.
C₈H₁₀O₂N₂Br Methyl 2-nitro-4-bromonitro-2-methylamyl ether, 1491.

- $C_7H_{11}ONCl$ *N*-Methyl-*N*-2-chloroethylmorpholine, salts, 532.
 $C_7H_{11}O_2NCl$ 6-Chlorohexyl carbamate, 179.
 Ethyl-2-ethoxyethylcarbamyl chloride, 313.
 $C_7H_{11}O_2NS$ Methyl 2:4-dinitro-2-methylamyl sulphide, 1492.
 $C_7H_{11}ONCl$ Di-(2-chloroethyl)-2-methoxyethylamine, and its salts, 529.
 Methyl-2-chloroethyl-2-(2-chloroethoxy) ethylamine, and its salts, 517, 532.
 $C_7H_{11}O_2NS$ 2-Nitropropyl butyl sulphide, 1479.
 $C_7H_{11}O_2NS$ 2-Nitropropyl butyl sulphone, 1479.
 $C_7H_{11}O_2NS$ 1-Amino-1-carbethoxy-2-methylpropanesulphonic acid, and its sodium salt, 1484.
 $C_7H_{11}NClS$ 4-β-Chloroethylthiomorpholine methochloride, 60.
 $C_7H_{11}O_2NCl$ Trimethyl-3-hydroxypropylammonium chloride urethane, 180.
 $C_7H_{11}ONCl$ Dimethyl-β-hydroxyethylisopropylammonium chloride, 59.
 $C_7H_{11}ONBr$ 3-Dimethylamino-2:2-dimethylpropanol hydrobromide, 59.

7 V

- $C_7H_{11}ONClS$ *N*-β-Hydroxyethylthiomorpholine methochloride, 60.
 $C_7H_{11}ONIS$ Trimethyl-2-hydroxyethylammonium iodide *N*-methylthiourethane, 181.

C₈ Group.

- C_8H_9N 3:5-Dicyanobenzidine, 83.
 $C_8H_6O_4$ Anhydrotetronic acid, structure of, 1365.
 $C_8H_8O_4$ β-2-Furoylpropionic acid, 1194.
 C_8H_7N 2-α-Pyridyldihydroglyoxaline, and its salts, 500.
 2-β-Pyridyldihydroglyoxaline, and its salts, 500.
 $C_8H_{10}O_2$ Octa-3:5-diyne-1:8-diol, 1582.
 $C_8H_8O_2$ 3-Hydroxy-2-methoxy-4-methylpenta-1:3-diene-1-carboxylic lactone, 807.
 3-Hydroxy-2-methoxy-4-methylpenta-1:4-diene-1-carboxylic lactone, 807.
 Methyl 3-hydroxy-4-methylpent-4-en-1-yne-1-carboxylate, 807.
 $C_8H_{10}O_4$ *n*- and *iso*-Propyl aconates, 1178.
 $C_8H_{10}N_2$ *N*-Methylbenzamidine, benzenesulphonate, 385.
 Phenylacetamidine, picrate, 392.
 $C_8H_{11}O$ 5:6-Dihydro-*m*- and -*p*-tolyl methyl ethers, 1646.
 $C_8H_{11}O_2$ 2:5-Dihydroquinol dimethyl ether, 105.
 2:5-Dihydroresorcinol dimethyl ether, 105.
 3:6-Dihydroveratrole, 105.
 $C_8H_{11}O_4$ Dihydropenicillic acid, 807.
 $C_8H_{11}O$ 1-Methoxy-4-methylcyclohexene, 1647.
 $C_8H_{11}O_2$ Methyl 2-methylcyclopentan-1-ol-1-carboxylate, 1567.
 $C_8H_{11}N_2$ 1:2-Bis-(2'-dihydroglyoxalyl)ethane, and its toluene-*p*-sulphonate, 500.
 $C_8H_{11}O$ 1-Butoxy-2-methylpropene, 1647.
 $C_8H_{10}O_2$ 2:3-Dimethyl galactonic acid, 1625.
 $C_8H_{10}N_2$ 5-Methylimino-1:2:2-trimethylpyrrolidine, and its picrate, 1511.
 $C_8H_{11}N_2$ α-Amidinoheptane, picrate, 392.
 1:1-Di(aminomethyl)cyclohexane, 1519.
 α-Ethyl-α-*n*-butylacetamidine, and its picrate, 741.
 $C_8H_{11}N$ 4-Amino-3:3-dimethylhexane, 1497.

8 III

- $C_8H_7N_3Cl_3$ 4:6:7-Trichlorocinnoline, 232.
 4:7:8-Trichlorocinnoline, 231.
 $C_8H_9O_3N_3$ 2:4:6-Trinitro-2':2':2'-trinitroethylbenzene, 1236.
 $C_8H_7OCl_3$ 2:3:4-Trichloroacetophenone, 231.
 $C_8H_7O_3I_3$ 3:4:5-Tri-iodophenylacetic acid, 203.
 $C_8H_7O_2N_3$ 5-Nitro-3-cyanobenzamide, 83.
 $C_8H_7O_2Br$ Bromoanhydrotetronic acid, 1368.
 $C_8H_7O_3I_2$ 3:5-Di-iodophenylacetic acid, 203.
 $C_8H_7O_2N_3$ 3-Nitro-4-cyanoanisole, 440.
 $C_8H_7O_3I_2$ 3:5-Di-iodo-2-hydroxyphenylacetic acid, 203.
 $C_8H_7O_2N_3$ 4-Nitro-2':2':2'-trinitroethylbenzene, 1236.
 C_8H_7OBr 5-Bromo-*o*-tolualdehyde, 692.
 $C_8H_7O_2N$ α-2-Furoylpropionitrile, 1194.
 $C_8H_7O_2N$ 2-Cyano-5-acetoxymethylfuran, 398.
 C_8H_7ClBr 4-Chloro-*o*-xylylene dibromide, 668.
 C_8H_7ON *p*-Methoxyphenylcyanamide, 916.
 $C_8H_7O_2N$ 4-Cyano-*m*-anisidine, 440.
 3-Keto-6-(2'-furyl)-2:3:4:5-tetrahydropyridazine, 1194.
 $C_8H_7O_2N_2$ 2-Nitro-4-formamidotoluene, 249.
 $C_8H_7O_2N_2$ 2-Nitro-4-methoxybenzamide, 894.
 C_8H_7NCl *p*-Chlorobenzylmethyleneimine, 1118.
 C_8H_7NS 4-(2'-Pyrrolyl)-2-methylthiazole, 1659.
 C_8H_7ClBr 3(or 4)-Chloro-*o*-xylyl bromide, 668.
 C_8H_7ClAs 2-Chloroisocarsindoline, 667.
 C_8H_7IAs 2-Iodoisocarsindoline, 667.
 C_8H_7ON *p*-Carbamidobenzamidine, salts, 392, 393.
 C_8H_7OBr *o*-Bromobenzyl methyl ether, 1639.
 $C_8H_7O_2N$ Anisamide, oxalate, 100.
 $C_8H_7O_2N_2$ *N*-Methyl-*p*-nitrobenzamidine, and its picrate, 1113.
 2-(2'-Nitrophenyl)dihydroglyoxaline, and its picrate, 500.

- $C_8H_8O_2As$ *o*-Xylylenearsinic acid, and its nitrate, 667.
 $C_8H_8O_2N$ 3-Methoxy-6-methylpicolinic acid, 133.
 C_8H_8ON 2-Amino-4-formamidotoluene, 249.
 $C_8H_8O_2N$ 4-Methoxyanthranilamide, 894.
 2-Nitroethylaniline, and its hydrochloride, 1488.
 $C_8H_{10}O_2N$ Methyl 4-methylpyrazole-3:5-dicarboxylate, 1033.
 $C_8H_{10}N_2S$ Bis-(2-amino-4-thiazolylmethyl)disulphide, 324.
 $C_8H_{11}ON$ 1-(1-Nitrovinyl)cyclohexene, and its dimer, 1474.
 $C_8H_{11}ON$ 5-Acetamido-4-hydroxy-2:6-dimethylpyrimidine, 50.
 $C_8H_{12}ON$ 2-Ethoxy-3:6-dimethylpyrazine, and its picrate, 1182.
 $C_8H_{12}N_2S$ 5:5'-Methylcyclo-tetramethylene-2:4-dithiohydantoin, 683.
 5:5'-cycloPentamethylene-2:4-dithiohydantoin, 683.
 $C_8H_{13}ON$ 1-Dimethylamino-4-acetoxyprop-2-yne, and its methiodide, 1579.
 $C_8H_{13}ON$ 1-(1-Nitro-2-hydroxyethyl)cyclohexene, 1474.
 $C_8H_{13}ON$ 5-Keto-2-ethoxy-3-acetyl-2-methyltetrahydro-oxazole, 100.
 $C_8H_{13}N_2S$ 2:2-Dithiocyanotriethylamine, hydrochloride, 322.
 $C_8H_{14}OS$ cycloHexyl thiolacetate, 138.
 $C_8H_{14}O_2S$ cycloHexylthioglycollic acid, 39.
 $C_8H_{14}ON$ 1:1-Di(nitromethyl)cyclohexane, 1519.
 $C_8H_{14}O_2S$ cycloHexylglycolyl sulphone, 39.
 $C_8H_{14}O_2S$ 2:5-Bismethanesulphonyl 1:4:3:6-dianhydro-*D*-iditol, 1405.
 2:5-Bismethanesulphonyl 1:4:3:6-dianhydro-*L*-iditol, 1404.
 $C_8H_{14}N_2S_2$ 5-Methyl-5-isobutyl-2:4-dithiohydantoin, 683.
 5-Methyl-5-*tert*-butyl-2:4-dithiohydantoin, 683.
 $C_8H_{15}ON$ Ethyl isopropoxymethyleneaminoacetate, 101.
 $C_8H_{15}OCl$ 3-Chloro-4:6-benzylidene-2-methyl α -methylglucoside, 16.
 $C_8H_{15}ON$ 2-Methyl α -methyl- β -galacturonoside amide, 1340.
 $C_8H_{16}OS$ cycloHexyl ethyl sulphone, 1550.
 $C_8H_{16}O_2S$ 3-Ketodibutyl sulphone, 1516.
 $C_8H_{16}O_2S$ 6-Methyl β -methylgalactoside sulphate, barium salt, 1678.
 $C_8H_{17}ON$ *trans*-2-Dimethylaminocyclohexanol, and its salts, 167.
 3:3-Dimethylhexan-4-one oxime, 1497.
 Methyl dimethylamino-*tert*-butyl ketone, picrate, 59.
 $C_8H_{17}ON$ 2-Nitro-3-*n*-butoxy-*n*-butyl alcohol, 1477.
 $C_8H_{18}NCl$ 3-Chloro-1-dimethylamino-2:2-dimethyl-*n*-butane, picrate, 59.
 $C_8H_{18}Cl_2Sn$ Di-*n*-butyldichlorotin, 1450.
 $C_8H_{18}ON$ Heptoxyguanidine, nitrate, 967.
 $C_8H_{18}ON$ Hexoxydiguamide, nitrate, 966.
 $C_8H_{19}ON$ 2-Amino-3-*n*-butoxy-*n*-butyl alcohol, 1477.
 Di-2-ethoxyethylamine, and its picrolonate, 313.
 $C_8H_{19}O_2P$ Diethyl *n*-butylphosphonate, 1466.
 $C_8H_{19}N_2S_2$ Ethyldi-(2-*isothioureido-S*-ethyl)amine, and its trihydrochloride, 322.
 $C_8H_{20}O_2N$ 1:6-Hexamethylenedioxydiguamide, dinitrate, 967.

8 IV

- C_8H_8ONCl 6:7-Dichloro-4-hydroxycinnoline, 232.
 7:8-Dichloro-4-hydroxycinnoline, 231.
 C_8H_8ONCl 2-Chloro-5-cyanobenzoic acid, 640.
 $C_8H_8ON_2Cl$ 7-Chloro-6- and -8-nitro-4-hydroxycinnolines, 236.
 $C_8H_8ON_2Cl$ 7-Chloro-4-hydroxycinnoline, 236.
 $C_8H_8ON_2Cl$ 3:4-Dichloro-2-nitroacetophenone, 231.
 C_8H_8ONS 2-Methylthio-4-(2'-furyl)thiazole, and its hydrobromide, 1658.
 C_8H_8OClBr 5-Bromo-*o*-toluoyl chloride, 690.
 C_8H_8ONCl 4-Chloro-2-nitroacetophenone, 236.
 C_8H_8ONS 4-(2'-Furyl)-2-methylthiazole, and its hydrobromide, 1658.
 β -2-Thienoylpropionitrile, 1194.
 C_8H_8ONCl 6-Chloro-4-hydroxydihydroquinazoline, 895.
 C_8H_8OClS Phenyl chlorothiolacetate, 559.
 C_8H_8ONBr $\omega\omega'$ -Dibromo-5-nitro-*m*-xylene, 1236.
 $C_8H_8ON_2I$ 3:5-Di-iodo-4-aminophenylacetic acid, 203.
 $\omega\omega'$ -Di-iodo-5-nitro-*m*-xylene, 1236.
 $C_8H_8ON_2Cl$ 4-Chloro-2-nitro-3-aminoacetophenone, 231.
 4-Chloro-2-nitro-5-aminoacetophenone, 231.
 4-Chloro-3- and -5-nitro-2-aminoacetophenones, 236.
 $C_8H_8ON_2S$ 2:4-Dinitrophenyl-2-nitroethyl sulphide, 1480.
 $C_8H_8Cl_2As$ 5-Chloro-2-iodo-*iso*arsindoline, 668.
 C_8H_8ONCl 4-Chloro-2-aminoacetophenone, 235.
 C_8H_8ONBr ω -Bromo-5-nitro-*m*-xylene, 1236.
 C_8H_8ONBr 5-Bromo-*o*-toluoylhydrazide, 691.
 $C_8H_8ON_2Cl$ 4-Chloro-3-nitrodimethylaniline, and its methiodide, 187.
 C_8H_8ONS 1-Nitro-2-phenylethane-2-sulphonic acid, sodium salt, 1484.
 C_8H_8ONCl 2-Chloro-5-dimethylaminophenol, 188.
 $C_8H_{10}ONCl$ 4-Chloro-5-acetamido-2:6-dimethylpyrimidine, 50.
 $C_8H_{10}ON_2S$ *m*-Aminodiphenylmethyl sulphone, thiocyanate, 392.
 p -Aminodiphenyl methyl sulphone, 394.
 $C_8H_{10}ON_2S_2$ 2-Diacetamido-4-mercaptomethylthiazole, 324.
 $C_8H_{10}ON_2S$ 5-Acetamido-4-carbethoxythiazole, 1598.
 $C_8H_{11}OCl_2S$ cycloHexyl trichlorothiolacetate, 141.
 $C_8H_{11}O_2NS$ 1-Amino-2-phenylethane-2-sulphonic acid, 1484.

- $C_5H_{11}ON_2S$ 5:5-*cyclo*Pentamethylene-2-thiohydantoin, 686.
 5:5-*cyclo*Pentamethylene-4-thiohydantoin, 686.
 $C_6H_{11}OCl_2S$ *cyclo*Hexyl dichlorothioliacetate, 140.
 $C_6H_{11}O_2N_2S$ Ethyl 2-amino-4-methylthiazole-5-acetate, 591.
 $C_6H_{11}O_2N_2S$ β -Sulphanilyl- α -methylguanidine, 821.
 $C_6H_{11}OClS$ *cyclo*Hexyl chlorothioliacetate, 139.
 $C_6H_{10}O_2N_2S$ Di(nitro-*tert.*-butyl) sulphide, 1480.
 Di-(2-nitro-1-methylpropyl) sulphide, 1481.
 $C_6H_{10}O_2N_2S$ Di(nitro-*tert.*-butyl) sulphone, 1481.
 Di-(2-nitro-1-methylpropyl) sulphone, 1481.
 $C_6H_{11}O_2NS$ *n*-Butyl nitro-*tert.*-butyl sulphide, 1479.
 $C_6H_{11}O_2N_2Cl$ *N*-2-Hydroxyethylmorpholine methochloride urethane, 181.
 $C_6H_{11}O_2NS$ 1-Nitro-2:4:4-trimethylpentane-2-sulphonic acid, sodium salt, 1485.
 $C_6H_{11}NCl_2$ β -Chloroethylpiperidine methiodide, 59.
 1:1-Dimethyl-3-chloromethylpiperidinium iodide, 59.
 $C_6H_{11}ONBr$ Methyl dimethylamino-*tert.*-butyl ketone hydrobromide, 59.
 $C_6H_{11}ONS$ 3-Aminodibutyl sulphone, and its hydrochloride, 1516.
 $C_6H_{11}O_2N_2Cl$ Trimethyl-4-hydroxybutylammonium chloride urethane, 180.
 $C_6H_{11}O_2N_2I$ Trimethyl-2-hydroxyethylammonium iodide *N*-dimethylurethane, 180.
 $C_6H_{10}OCl_2Si$ Tetraethyldichlorodisiloxane, 1591.

C₉ Group.

- C_9H_8 Indene, isolation of, from heavy naphtha, 369.

9 II

- C_9H_8O Anhydrotetronic acid methyl ether, 1368.
 C_9H_7N 1-Phenyliminazole, and its picrate, 102.
 $C_9H_7I_3$ $\omega\omega'\omega''$ -Tri-iodomesitylene, 1237.
 $C_9H_{10}O_2$ Homovanillin, 1692.
 $C_9H_{10}O_4$ *n*- and *iso*-Propyl coumalates, 1178.
 $C_9H_{10}N_2$ 2-Phenyldihydroglyoxaline, and its salts, 500, 504.
 $C_9H_{11}N_3$ 2- α -Pyridyl-3:4:5:6-tetrahydropyrimidine and its picrate, 500.
 $C_9H_{11}O_2$ Catechol *isopropyl* ether, 104.
 2-Ketocyclohexyl- α -propionolactone, 1164.
 $C_9H_{11}O_4$ *n*- and *iso*-Butyl aconates, 1178.
 Methyl penicillate, 807.
 $C_9H_{11}N_3$ *NN'*-Dimethylbenzamidine, sulphamate, 385, 504.
N-Ethylbenzamidine, salts, 385.
 $C_9H_{11}O$ Non-2-en-4-yn-1-ol, 1585.
 $C_9H_{11}O_2$ 4-Methyl-3:6-dihydroveratrole, 105.
 $C_9H_{11}P$ Triallylphosphine, 1448.
 $C_9H_{11}O$ 2:2:3-Trimethylcyclohexanone, 1567.
 $C_9H_{11}O_2$ 3:4-Acetone β -methyl-*L*-arabinoside, 1343.
 2-Methyl acetone *L*-arabinose, 1344.
 3-Methyl 1:2-acetone *L*-arabinose, 1063.
 3:4-*iso*Propylidene β -methyl-*L*-arabopyranoside, 971.
 $C_9H_{11}O_7$ 2-Methyl α -methyl-*D*-galacturonoside methyl ester, 1340.
 $C_9H_{11}N_4$ 1:3-Bis-(2'-dihydroglyoxaliny)propane, and its toluene-*p*-sulphonate, 500.
 $C_9H_{11}S$ Geraniolene sulphide, 1529.
 $C_9H_{11}O_2$ $\alpha\alpha\beta\beta$ -Tetramethylvaleric acid, 1498.
 $C_9H_{11}O_2$ Methyl $\alpha\beta$ -diethoxypropionate, 1032.
 $C_9H_{11}N_2$ 2:2:4:4:6-Pentamethyl-2:3:4:5-tetrahydropyrimidine, and its hydrate, and its oxalate, 1397.
 $C_9H_{11}S_2$ Geraniolene disulphide, 1538.
 $C_9H_{11}N_2$ *NN*-Diethyl-*n*-valeramidine, picrate, 395.
 2:2:4:4:6-Pentamethylhexahydropyrimidine, 1398.
 $C_9H_{10}Sn$ Triethylallyltin, 1450.
 $C_9H_{11}N_2$ *s*-Tetraethylguanidine, and its picrate, 396.
 $C_9H_{11}N$ Amino-*isopropyl*amino-2-methylpentane, and its dihydrochloride, 1398.

9 III

- C_9H_7OCl *o*-Chlorophenyl ethynyl ketone, 1630.
 $C_9H_7O_2N$ 6-Nitro-3-methoxyphthalic anhydride, 354.
 $C_9H_7N_2Cl$ 2:4-Dichloro-6-*p*-chloroanilino-1:3:5-triazine, 158.
 $C_9H_7O_2N_2$ 5- and 7-Nitroquinolines, and their salts, 442.
 $C_9H_7O_2N_2$ Methyl 5-nitro-3-cyanobenzoate, 83.
 C_9H_7NCl 4-Chloroquinoline, and its salts, 440.
 7-Chloroquinoline, and its salts, 441, 443.
 C_9H_7NBr 5-Bromoquinoline, and its salts, 440.
 7-Bromoquinoline, and its salts, 441.
 C_9H_7ON 5-Hydroxyquinoline, and its salts, 440.
 7-Hydroxyquinoline, and its salts, 441.
 C_9H_7OCl *o*-Chlorophenylethynylcarbinol, 1630.
 $C_9H_7O_2N$ 5-Nitroindene, and its polymer, 95.
 Pyrrocoline-2-carboxylic acid, 674.
 $C_9H_7O_2N$ 6-Nitro-3-methoxyphthalic acid, 355.
 $C_9H_7N_2Cl$ 8-Chloro-6-aminoquinoline, 679.
 6-Chloro-4-methylcinnoiline, and its picrate, 811.
 7-Chloro-4-methylcinnoiline, 811.

- C_6H_5ON Benamidomethyl cyanide, 1371.
 $C_6H_5O_2N$ 2:4-Dihydroxy-7-methoxyquinazoline, 899.
 $C_6H_5O_2N$ 5-Nitro-*ON*-diacetylindoxyl, 611.
 $C_6H_5O_2N$ Malonic semi-aldehyde 2:4-dinitrophenylhydrazones, 1032.
 $C_6H_5N_2S$ 5-Amino-4-phenylthiazole, and its hydrochloride, 1598.
 $C_6H_5N_2S$ 5-Amino-2-mercapto-4-phenylthiazole, and its hydrochloride, 1603.
 $C_6H_5N_2S$ 2:4-Dithio-5-phenylhydantoin, 1606.
 $C_6H_5N_2Cl$ 2-Chloro-7-amino-4-methyl-1:8-naphthyridine, 1409.
 $C_6H_5O_2Br$ 5-Bromo-2-hydroxy-4-methylacetophenone, 230.
 $C_6H_5O_2Br$ 5-Bromo-*o*-tolylacetic acid, 691.
 $C_6H_5O_2N$ 6-Nitro-1-hydrindenol, 95.
 $C_6H_5N_2Cl$ 2-(4'-Chlorophenyl)dihydroglyoxaline, and its salts, 500.
 C_6H_5ON 2-*p*-Hydroxyphenyldihydroglyoxaline, and its salts, 504.
 $C_6H_5O_2N$ 2-Nitro-3-amino-4-methylacetophenone, 230.
 $C_6H_5O_2N$ 2-Nitro-5-amino-4-methylacetophenone, 230.
 $C_6H_5O_2N$ 3-Nitro-5-amino-4-methylacetophenone, 229.
 $C_6H_5O_2N$ 2-Carbamido-4-methoxybenzoic acid, 898.
 C_6H_5ClAs 5-Chloro-2-methylisarsindoline, and its salts, 669.
 C_6H_5ON Benamidoacetamidine, hydrochloride, 1374.
 $C_6H_5O_2N$ 3-Nitro-4-*isopropylphenol*, 186.
 $C_6H_5O_2N$ β -(3:4-Dihydroxyphenyl)serine, and its picrate, 660.
 C_6H_5OS Methyl 2-phenoxyethyl sulphide, 770.
 $C_6H_5O_2N$ 3-Dimethylaminophenol urethane, methiodide, 189.
 $C_6H_5O_2N$ Methyl-2-nitroethylamine, hydrochloride, 1489.
 $C_6H_5O_2N$ 2-Nitro-4-aminoisopropylbenzene, 186.
 $C_6H_5O_2N$ 3-Nitro-5-dimethylaminotoluene, methiodide, 187.
 $C_6H_5O_2N$ 2-Nitroisopropylamine, 1489.
 $C_6H_5N_2S$ 2:2':2''-Trithiocyanotriethylamine, hydrochloride, 322.
 C_6H_5ON 3-Amino-4-*isopropylphenol*, 186.
 C_6H_5ON 4-Dimethylamino-*o*-cresol, and its methiodide, 188.
 C_6H_5ON 5-Dimethylamino-*m*-cresol, 188.
 C_6H_5ON 2-Dimethylamino-*p*-cresol, and its methiodide, 188.
 C_6H_5ON 3-Ureidophenyldimethylamine, and its methiodide, 185.
 $C_6H_5O_2N$ 5-Methoxy-2-methyl-6-methoxymethylpyridine, picrate, 133.
 $C_6H_5O_2Br$ Diethyl γ -bromomesaconate, 1179.
 $C_6H_5O_2N$ Cytidine, synthesis of, 1052.
 C_6H_5NS *p*-Tolyl 2-aminoethyl sulphide, hydrochloride, 1481.
 $C_6H_5O_2N$ 1-Nitro-1-(2-cyanoethyl)cyclohexane, 1507.
 $C_6H_5N_2S$ 5:5-*cyclohexamethylene*-2:4-dithiohydantoin, 683.
 $C_6H_5N_2S$ 5:5-Methylcyclopentamethylene-2:4-dithiohydantoins, 683.
 $C_6H_5O_2N$ Ethyl α -(α -ethoxyethylideneamino)- β -hydroxyacrylate, potassium salt, 101.
 $C_6H_5O_2N$ Ethyl α -isopropoxymethyleneamino- β -hydroxyacrylate, potassium salt, 101.
 $C_6H_5O_2N$ 3-Nitro-2:4-diacetoxypentane, 1473.
 C_6H_5ON 5-Amino-2:2-pentamethylenepyrroline *N*-oxide, and its hydrochloride, 1511.
 C_6H_5OS 2-Methylcyclohexyl thiolacetate, 138.
 C_6H_5OS 2:2-Pentamethylene-4-hydroxymethyl-1:3-dithiolan, 595.
 $C_6H_5O_2Cl$ 8-Chloro-octyl chloroformate, 178.
 $C_6H_5O_2Br$ 1-Bromo-3-(2-bromoethyl)hexane-1-carboxylic acid, 224.
 $C_6H_5O_2S$ Methylcyclohexylthioglycolic acids, 39.
 $C_6H_5O_2N$ Nitro-2-(1-nitroisopropyl)cyclohexane, 1491.
 $C_6H_5O_2S$ 1-Methylcyclohexylglycolyl sulphones, 39.
 $C_6H_5N_2S$ 5-Methyl-5-*n*-amyl-2:4-dithiohydantoin, 683.
 $C_6H_5O_2N$ 2-Nitroisopropylcyclohexane, 1499.
 $C_6H_5O_2Br$ 3-(2-Bromoethyl)hexane-1-carboxylic acid, 224.
 $C_6H_5O_2N$ Methyl 8-ketoheptate semicarbazone, 1108.
 C_6H_5ON 1:3-Di-*n*-propyliminazolid-2-one, 315.
 $C_6H_5O_2S$ *n*-Butyl 3-ketoamyl sulphone, 1516.
 $C_6H_5O_2N$ 1-Nitro-2:2:3:3-tetramethylpentane, 1498.
 $C_6H_5O_2N$ Hexoxyurethane, 966.
 $C_6H_5O_2N$ Nitro-*tert*-butyl *n*-amyl ether, 1476.
 $C_6H_5NCl_2$ β -Chloroethylideneisopropylamine hydrochloride, 59.
 C_6H_5ON Nonoxyamine, salts, 967.
 $C_6H_5O_2P$ Diethyl *n*-amylphosphonate, 1466.
 $C_6H_5O_2P$ Diethyl 3-methyl-*n*-butyl-1-phosphonate, 1467.
 $C_6H_5N_2S$ Tri-(2-isothioureido-*S*-ethyl)amine, tetrahydrochloride, 322.
 $C_6H_5O_2P$ Tetraethyl methylenediphosphonate, 1467.

9 IV

- C_6H_5ONCl 2:4-Dichloro-7-methoxyquinazoline, 899.
 C_6H_5ONCl 6-Chloro-4-hydroxy-7-methylcinnoline, 230.
 C_6H_5ONCl 8-Chloro-4-hydroxy-7-methylcinnoline, 231.
 C_6H_5ONCl 4-Chloro-6-methoxycinnoline, 920.
 C_6H_5ONCl 6-Chloro-4-methoxycinnoline, 1655.
 C_6H_5ONCl 6-Chloro-1-methyl-4-cinnolone, 1655.
 C_6H_5ONBr 6-Bromo-4-hydroxy-7-methylcinnoline, 230.
 $C_6H_5O_2N$ *p*-Nitrophenyl 2-amino-5-thiazyl sulphide, 112.
 C_6H_5NClS 2-Chloro-4-methylthioquinazoline, 780.
 C_6H_5NClS 2-*p*-Chlorobenzenesulphenamidothiazole, 113.
 C_6H_5NClS *p*-Chlorophenyl 2-acetamido-5-thiazyl sulphide, 113.

- $C_8H_7N_2BrS$ 5-Bromo-2-amino-4-phenylthiazole, 118.
 $C_8H_7ON_2Br$ 5-Bromo-*o*-tolyl diazomethyl ketone, 690.
 $C_8H_7O_2NCl$ 3-Chloro-2-nitro-4-methylacetophenone, 230.
 $C_8H_7O_2N$ 5-Chloro-2-nitro-4-methylacetophenone, 230.
 $C_8H_7O_2NBr$ 5-Bromo-2-nitro-4-methylacetophenone, 230.
 C_8H_7ONS 2-Methyldihydro-1:3-benzthiazine-4-one, 764.
 $C_8H_7O_2ClSb$ *p*-Carbethoxyphenylstibinous chloride, 8.
 $C_8H_7O_2ISb$ *p*-Carbethoxyphenyl stibinous iodide, 8.
 $C_8H_7O_2NS$ 2-Methyldihydro-1:3-benzthiazine-4-one *S*-dioxide, 764.
 $C_8H_7N_2Cl$ 6-Chloro-4-aminocinnoline methiodide, 1655.
 C_8H_7ONCl 5-Chloro-2-amino-4-methylacetophenone, 230.
 C_8H_7ONBr 5-Bromo-2-amino-4-methylacetophenone, 230.
 $C_8H_7ON_2S$ Benzamidothioacetamide, 1373.
 $C_8H_7ON_2Br$ 5-Bromo-*o*-tolualdehyde semicarbazone, 692.
 $C_8H_7ON_2S$ 2-(4'-Sulphophenyl)dihydroglyoxaline, 500.
 $C_8H_7OS_2As$ 5-Hydroxy-2-phenyl-1:3-dithia-2-arsacyclohexane, 595.
 $C_8H_7O_2NS$ 2-Phenyl-4-hydroxymethyl-1:3-dithia-2-arsacyclopentane, 595.
 $C_8H_7O_2NS$ Methyl 2-nitro-1-phenylethyl sulphide, 1479.
 $C_8H_7O_2NS$ Phenyl 2-nitroisopropyl sulphide, 1479.
 $C_8H_7O_2N_2S$ 2-(4'-Sulphonamidophenyl)dihydroglyoxaline, and its toluene-*p*-sulphonate, 500.
 $C_8H_7O_2N_2S$ *p*-Methylsulphonylbenzamidinium thiocyanate, 391.
 $C_8H_7O_2NS$ *N*-Acetylbenzenesulphonmethylamide, 387.
 $C_8H_7O_2NS$ *p*-Tolyl 2-nitroethyl sulphone, 1481.
 C_8H_7ONCl 5-Chloro-2-aminophenyldimethylcarbinol, 810.
 $C_8H_7O_2N_2S$ 2-*p*-Aminobenzenesulphonamidoinnazoline, 822.
 $C_8H_7O_2NS$ β -Sulphanilyl- α -acetylguanidine, 822.
 $C_8H_7Cl_2S_2Hg$ Phenyl 2-methylthioethyl sulphide mercurichloride, 772.
 $C_8H_7O_2ClS$ 2-Methylcyclohexyl trichlorothioloacetate, 141.
 $C_8H_7O_2NS$ Ethyl 2:4-dimethylthiazole-5-acetate, and its picrate, 1402.
 $C_8H_7O_2N_2P$ Uridine-2'-phosphate, and its salts, 341.
 $C_8H_7O_2N_2S$ β -Sulphanilyl- α -dimethylguanidine, 821.
 $C_8H_7O_2ClS$ 2-Methylcyclohexyl chlorothioloacetate, 139.
 $C_8H_7O_2NCl$ Di-(2-ethoxyethyl)carbamyli chloride, 313.
 C_8H_7NClS 2-Chloroethyl 2-(*N*-diethyldithiocarbamate)ethyl sulphide, 850.
 $C_8H_7O_2N_2Cl$ Trimethyl-2-hydroxyethylammonium chloride *N*-allylurethane, 180.
 $C_8H_7O_2N_2Cl$ Trimethyl-2-hydroxyethylammonium chloride *N*-propylurethane, 180.
 $C_8H_7O_2N_2I$ Trimethyl-5-hydroxypentylammonium chloride urethane, 180.
 $C_8H_7O_2N_2I$ Triethyl-2-hydroxyethylammonium iodide urethane, 181.

9 V

- $C_8H_7O_2N_2ClS$ *p*-Chlorophenyl 2-amino-5-thiazyl sulphone, 114.
 $C_8H_7O_2NBrS$ 3-Bromo-1-*p*-nitrobenzenesulphonylacetone, 117.
 $C_8H_7O_2NBrS$ *n*-Butyl 3-bromo-3-nitroamyl sulphone, 1516.

 C_{10} Group.

- $C_{10}H_8$ Naphthalene, chloromethylation of, 1432.
 $C_{10}H_{11}$ Tetrahydronaphthalene, chloromethylation of, 1432.

10 II

- $C_{10}H_{11}N$ 1- α -Phenylethyldimethylamine, and its picrate, 94.
 $C_{10}H_8O_4$ Octa-1:7-dien-3:5-diyne-1:8-dicarboxylic acid, 1589.
 $C_{10}H_7N_2$ 5-Cyanoquinoline, and its salts, 439.
 $C_{10}H_7N_2$ 7-Cyanoquinoline, and its salts, 441.
 $C_{10}H_6I_2$ 1:5-Di-iodonaphthalene, 81.
 $C_{10}H_7O$ *m*-Methoxyphenyl ethynyl ketone, 348.
 $C_{10}H_7O$ *o*-Methoxyphenylpropionic acid, dimerisation of, 224.
 $C_{10}H_7F$ *p*-Fluorophenylbutadiene, 1095.
 $C_{10}H_7Cl$ 1-(*p*-Chlorophenyl)buta-1:3-diene, 1095.
 $C_{10}H_7Br$ 1-(*p*-Bromophenyl)buta-1:3-diene, 1095.
 $C_{10}H_8O_2$ Deca-2:8-dien-4:6-diyne-1:10-diol, 1589.
 $C_{10}H_7O$ *m*-Methoxyphenylethylnylcarbinol, 348.
 $C_{10}H_9O_4$ β -3-Hydroxybenzoylpropionic acid, 1193.
 $C_{10}H_7N_2$ 8-Amino-7-methylquinoline, 441.
 $C_{10}H_7N_2$ 1-Phenyl-2-methyliminazole, and its picrate, 102.
 $C_{10}H_{11}O_2$ Clavatol, 612.
 $C_{10}H_{11}O_2$ Pent-2-en-4-yn-1-ol, 1584.
 $C_{10}H_{11}O_4$ *n*- and *iso*-Butyl coumalates, 1178.
 $C_{10}H_{11}O_4$ Ethyl β -2-furoylpropionate, 1194.
 $C_{10}H_{11}N_2$ 2-Benzoyldihydroglyoxaline, and its salts, 500.
 $C_{10}H_{11}N_2$ 2-Phenyl-3:4:5:6-tetrahydropyrimidine, and its salts, 500.
 $C_{10}H_{11}N_2$ 2-(4'-Aminobenzyl)dihydroglyoxaline, and its salts, 500.
 $C_{10}H_{11}O_2$ Deca-4:6-diyne-2:9-diol, 1582.
 $C_{10}H_{11}O_2$ 2-(2:3-Epoxy-1-butoxy)hex-en-5-yne, 1585.
 $C_{10}H_{11}O_2$ *o*-2-Hydroxyethylbenzyl methyl ether, 1639.
 $C_{10}H_{11}O_2$ 2-Hydroxycyclohex-1-enyl- α -isobutyrolactone, 1166.
 $C_{10}H_{11}N_2$ *N*-Methyl-*N'*-ethylbenzamidine, and its salts, 385.
 $C_{10}H_6Br_2$ *trans*-4:4'-Dibromo-2:2'-dimethylstilbene, 692.

- $C_{10}H_{11}N$ 2-Amino-3-phenylbutane, 1499.
 1-Cyano-2:2:3-trimethylcyclohex-6-ene, 1567.
 $C_{10}H_{11}N_2$ 3:6-Diamino-1:2:7:8-dibenzocarbazole, dihydrochloride, 77.
 $C_{10}H_{10}O_2$ 2:2:3-Trimethylcyclohex-6-ene-1-carboxylic acid, 1567.
 $C_{10}H_{10}O_3$ 1:2-Dihydroxycyclohexyl- α -isobutyrolactone, 1165.
 2-Ketocyclohexyl- α -isobutyric acid, 1166.
 $C_{10}H_9Br_4$ β -Phellandrene tetrabromide, 1039.
 $C_{10}H_{10}O_3$ 3:5-Dimethyl acetone *l*-arabofuranose, 1064.
 2-Methyl 3:4-acetone β -methyl-D-arabopyranoside, 1343.
 2-Methyl 3:4-acetone β -methyl-L-arabopyranoside, 1343.
 $C_{10}H_{12}N_4$ 1:4-Bis-(2'-dihydroglyoxalanyl)butane, and its toluene-*p*-sulphonate, 500.
 1:2-Bis-(2'-tetrahydropyrimidyl)ethane, and its toluene-*p*-sulphonate, 500.
 $C_{10}H_{18}S$ Dihydromyrcene sulphide, 1528.
 Thiolaetyl rubber, 139.
 $C_{10}H_{19}N$ $\alpha\alpha$ -Diethyl- α -*n*-butylacetoneitrile, 741.
 $C_{10}H_{20}O$ 2:2:6-Trimethyl-6-ethyltetrahydropyran, 1108.
 $C_{10}H_{20}O_2$ 2-(2:3-Epoxy-1-butoxy)hexane, 1585.
 $C_{10}H_{20}N_4$ 4:4'-Bis-(dihydroglyoxalanyl)stilbene, and its toluene-*p*-sulphonate, 500.
 $C_{10}H_{20}N_6$ 2:6-Diamino-4- β -diethylaminoethylaminopyrimidine, and its picrate, 46.
 $C_{10}H_{20}S$ 2:3-Dimethyl-6-isopropyltetrahydrothiopyran, 1539.
 2:2:6:6-Tetramethyltetrahydrothiopyran, 1107.
 2:2:6-Trimethyl-6-ethyltetrahydrothiopyran, 1108.
 $C_{10}H_{20}Sn$ Diethyldiallyltin, 1450.
 $C_{10}H_{22}O_2$ 2:6-Dimethyloctane-2:6-diol, 1108.
 $C_{10}H_{22}N_2$ Decoamidine, hydrochloride, 741.
 $\alpha\alpha$ -Diethyl- α -*n*-butylacetamidine, and its picrate, 741.
 $C_{10}H_{22}S_2$ Dihydromyrceneethiol, 139.
 2:6-Dimercapto-2:6-dimethyloctane, 1538.

10 III

- $C_{10}H_6O_2N_4$ 2:4:6:8-Tetranitro-1:5-dihydroxynaphthalene, 353.
 $C_{10}H_6O_3N_4$ 2:4:6-Trinitro-1:5-dihydroxynaphthalene, 353.
 $C_{10}H_6O_4N_4$ 1:8-Dinitronaphthalene, preparation of, 1109.
 $C_{10}H_6O_5N_4$ 2:4-Dinitro-1:5-dihydroxynaphthalene, 353.
 2:6-Dinitro-1:5-dihydroxynaphthalene, 353.
 $C_{10}H_6O_6N_4$ Tetranitronaphthylenediamines, 81.
 $C_{10}H_6O_2N$ 7-Nitro-2-naphthol, 331.
 $C_{10}H_6O_4N_2$ 1:7-Dinitro-2-naphthylamine, 1061.
 $C_{10}H_6O_5N_2$ 5-Nitro-1:3-bis-2':2':2'-trinitroethylbenzene, 1236.
 $C_{10}H_6NCl_2$ 1:4-Dichloro-2-naphthylamine, 543.
 1:5-Dichloro-2-naphthylamine, 543.
 $C_{10}H_6NBr_2$ 7:8-Dibromo-2-naphthylamine, 329.
 $C_{10}H_6N_2Cl_2$ 4:6-Dichloro-2-amino-5-phenylpyrimidine, 1362.
 $C_{10}H_6O_5N_2$ 1:4-Bis-2':2':2'-trinitroethylbenzene, 1236.
 $C_{10}H_6NCl$ 7-Chloro-8-methylquinoline, and its salts, 442.
 Chloro-2-naphthylamines, 330, 548, 549.
 $C_{10}H_6NBr$ 6- and 7-Bromo-2-naphthylamines, 330.
 $C_{10}H_6NI$ 6- and 7-Iodo-2-naphthylamines, 330.
 $C_{10}H_6N_2Cl_2$ 4-Chloro-2-amino-6-*p*-chloroanilinopyrimidine, and its hydrochloride, 1361.
 $C_{10}H_6ON$ 5-Methoxyquinoline, and its picrate, 440.
 7-Methoxyquinoline, and its salts, 441, 444.
 $C_{10}H_6O_2N$ β -3- and -4-Hydroxybenzoylpropionitriles, 1193.
 Methyl pyrrocoline-2-carboxylate, 674.
 $C_{10}H_6O_2N_2$ 2-Amino-4-hydroxy-5-phenoxyypyrimidine, 46.
 Base, from nitration of *o*-acetamidooacetophenone, 238.
 $C_{10}H_6O_2Br$ 4-Bromo-2-methylcinnamic acid, 692.
 $C_{10}H_6O_2Br$ β -*p*-Bromobenzoylpropionic acid, 1193.
 $C_{10}H_6NS_2$ 2-Methylthio-4-phenylthiazole, and its hydrobromide, 1658.
 $C_{10}H_6N_2Cl$ 1-Chloro-2-naphthylhydrazine, 543.
 $C_{10}H_6ON_2$ Benzamidoethyl cyanides, 1371.
 $C_{10}H_6O_2S$ β -(Benzylthio)acrylic acid, 1033.
 $C_{10}H_6O_2N_2$ 3-Nitro-2-acetamidooacetophenone, 238.
 $C_{10}H_6N_2S$ 5-Amino-2-benzylthiazole, 1596.
 Phenylthionacetamidooacetoneitrile, and its hydrochloride, 1596.
 $C_{10}H_6N_2S_2$ 5-Amino-2-methylthio-4-phenylthiazole, and its salts, 1604.
 2-*p*-Toluenesulphenamidothiazole, 113.
 $C_{10}H_6N_2Cl$ 2-Tolyl 2-amino-5-thiazyl sulphide, 113.
 $C_{10}H_6N_2Cl$ 6-Amino-2-*p*-chloroanilino-4-methyl-1:3:5-triazine, 158.
 $C_{10}H_7OCl$ *p*-Chlorophenylpropenylcarbinol, 1095.
 $C_{10}H_7OBr$ *p*-Bromophenylpropenylcarbinol, 1095.
 $C_{10}H_7OBr$ *p*-Bromostyrylmethylcarbinol, 1095.
 $C_{10}H_7OF$ *p*-Fluorophenylpropenylcarbinol, 1095.
 $C_{10}H_7OF$ *p*-Fluorostyrylmethylcarbinol, 1095.
 $C_{10}H_{11}O_2N$ 1:2:3:4-Tetrahydroisocoumaralidinic acid, 129.
 $C_{10}H_{11}O_2N$ β -4-Hydroxybenzoylpropionamide, 1195.
 $C_{10}H_{11}O_2N$ 9-*d*-Mannopyranosidoadenine picrate, 357.
 $C_{10}H_{11}O_2N$ 4-Methylcinnoline-7-carboxylic acid, preparation of, 809.
 $C_{10}H_{11}NS$ 3-Ethyl-2-methylenebenzthiazoline, 956.

- $C_{10}H_{11}NSe$ 3-Ethyl-2-methylenebenzselenazoline, 956.
 $C_{10}H_{11}ClS_2$ 2-Phenyl-4-chloromethyl-1:3-dithiolan, 594.
 $C_{10}H_{11}ON_2$ 2-*p*-Anisylidihydroglyoxaline, and its salts, 500.
 $C_{10}H_{11}OS$ β -Benzylthiopropaldehyde, 1611.
 $C_{10}H_{11}OS_2$ 2-Phenyl-4-hydroxy-1:3-dithian, 594.
 $C_{10}H_{11}OS_2$ 2-Phenyl-4-hydroxymethyl-1:3-dithiolan, 594.
 $C_{10}H_{12}ON$ β -Benzamidopropionamide, 1376.
 $C_{10}H_{12}OS$ Methyl 2-benzoyloxyethyl sulphide, 769.
 $C_{10}H_{12}ON_2$ 2-Nitroethylacetanilide, 1488.
 $C_{10}H_{12}OS$ "Eugenol sultone", 127.
 $C_{10}H_{12}ON_2$ 9-*d*-Xylopyranosidoxanthine, 381.
 $C_{10}H_{12}ON$ 7-Hydroxy-1-methyl-1:2:3:4-tetrahydroquinoline, 186, 188.
 $C_{10}H_{12}ON_2$ β -Benzamidopropionamidine, hydrochloride, 1376.
 $C_{10}H_{12}OCl$ *o*-2-Chloroethylbenzyl methyl ether, 1640.
 $C_{10}H_{12}ON$ 5:6-Dihydroxy-2-methyltetrahydroisoquinoline, salts, 194.
 $C_{10}H_{12}ON$ 6:7-Dihydroxy-2-methyltetrahydroisoquinoline, hydrobromide, 194.
 $C_{10}H_{12}ON$ 4-Methoxybenzylacetoxime, 196.
 $C_{10}H_{12}ON$ 2-Methoxypropiphenone oxime, 196.
 $C_{10}H_{12}ON$ α -Amino- γ -(*p*-hydroxyphenyl)butyric acid, 1572.
 $C_{10}H_{12}ON$ Methyl 2-nitro-1-phenyl-*n*-propyl ether, 1476.
 $C_{10}H_{12}ON$ 5-Acetoxyethylfuran-2-iminoether, hydrochloride, 398.
 $C_{10}H_{12}ON_2$ Di-(2-nitroethyl)aniline, and its hydrochloride, 1488.
 $C_{10}H_{12}O_2As$ Phenyl-3-carboxy-*n*-propylarsonic acid, 623.
 $C_{10}H_{12}ON$ β -(3:4-Dihydroxyphenyl)-*N*-methylserine, 661.
 $C_{10}H_{12}O_2Cl$ 2-Chloro 3:4-diacetyl 1:6-anhydro β -altrose, 15.
 $C_{10}H_{12}ON_2$ 2-Dimethylaminophenol *N*-methylurethane, methiodide, 189.
 $C_{10}H_{12}ON_2$ 3-Dimethylaminophenol *N*-methylurethane, salts, 189.
 $C_{10}H_{12}ON_2$ 4-Dimethylaminophenol *N*-methylurethane, methiodide, 189.
 $C_{10}H_{12}ON_2$ Ethyl-2-nitroethylaniline, and its salts, 1489.
 $C_{10}H_{12}ON_2$ 2-Furyl β -dimethylaminoethyl ketone cyanohydrin, 1194.
 $C_{10}H_{12}ON_2$ Methyl-2-nitropropylanilines, and their salts, 1489.
 $C_{10}H_{12}ON_2$ 2-Nitro-4-dimethylamino-1-ethylbenzene, methiodide, 187.
 $C_{10}H_{12}ON_2$ 4-Nitro-6-dimethylamino-*m*-xylene, methiodide, 187.
 $C_{10}H_{12}OS$ 2-Hydroxy-3-methoxy-5-*n*-propylbenzenesulphonic acid, and its salts, 125.
 $C_{10}H_{12}OS$ 5-Hydroxy-4-methoxy-2-*n*-propylbenzenesulphonic acid, and its salts, 126.
 $C_{10}H_{12}ON_2$ 1-*d*-Arabinosidoglyoxaline-4:5-dicarboxamide, 380.
 $C_{10}H_{12}ON_2$ 1-*L*-Arabinosidoglyoxaline-4:5-dicarboxamide, 380.
 $C_{10}H_{12}ON_2$ 1-*d*-Xylopyranosidoglyoxaline-4:5-dicarboxamide, 381.
 $C_{10}H_{12}ON$ 3-Dimethylamino-4-ethylphenol, methiodide, 188.
 $C_{10}H_{12}ON$ 5-Dimethylamino-2-ethylphenol, and its methiodide, 188.
 $C_{10}H_{12}ON$ 6-Dimethylamino-*m*-4-xlenol, 188.
 $C_{10}H_{12}ON$ Dimethyl- β -(hydroxyphenyl)ethylamines, salts, 194.
 $C_{10}H_{12}ON$ α -(2-Methoxyphenyl)propylamine, picrate, 196.
 $C_{10}H_{12}ON$ Phenylidimethylaminomethylcarbinol, and its salts, 168.
 $C_{10}H_{12}OBr$ cycloHex-1-enyl- α -isobutyrobromolactone, 1165.
 $C_{10}H_{12}ON_2$ 1-Nitro-2-(2-furyl)hexane, 1500.
 $C_{10}H_{12}ON_2$ 1-(1-Nitro-2-acetoxyethyl)cyclohexene, 1474.
 $C_{10}H_{12}NS$ Methyl 2-benzylaminoethyl sulphide, and its salts, 771.
 $C_{10}H_{12}S_2P$ Triallylphosphine-carbon disulphide, 1448.
 $C_{10}H_{12}ON_2$ 2:4-Tetramethyldiaminophenol, dimethiodide, 188.
 $C_{10}H_{12}ON_2$ 2:6-Tetramethyldiaminophenol, dihydrochloride, 188.
 $C_{10}H_{12}N_2S_2$ Dimethylcyclopentamethylenes, 683.
 $C_{10}H_{12}ON_2$ 5-Methyl-5-isohexenyl-2:4-dithiohydantoin, 683.
 $C_{10}H_{12}ON_2$ 5-Methyl-5-cyclohexyl-2:4-dithiohydantoin, 683.
 $C_{10}H_{12}ON$ 1-Diethylaminohex-4-en-2-yn-6-ol, 1579.
 $C_{10}H_{12}ON_2$ 2:2'-Hydroxyethylimino-5:5-cyclopentamethylenehydantoin, 686.
 $C_{10}H_{12}ON_2$ 4:2'-Hydroxyethylimino-5:5-cyclopentamethylenehydantoin, 686.
 $C_{10}H_{12}ON$ Ethyl ethoxycarbethoxymethyleneaminoacetate, 100.
 $C_{10}H_{12}O_2Cl$ 2-Chloro-3:4-acetone α -methylaltroside, 15.
 $C_{10}H_{12}O_2Br$ 2-Bromo-3:4-acetone α -methylaltroside, 17.
 $C_{10}H_{12}OS$ 3-Methyl-1:2-acetone glucofuranose 6-sulphate, barium salt, 1677.
 $C_{10}H_{12}O_2Cl$ 9-Chlorononyl chloroformate, 178.
 $C_{10}H_{12}OS$ 2-Methanesulphonyl 3:4-acetone β -methyl-D-arabinoside, 1343.
 $C_{10}H_{12}IP$ Methyltriallylphosphonium iodide, 1448.
 $C_{10}H_{12}ON$ 1-Diethylaminohex-2-yn-5-ol, and its picrate, 1579.
 $C_{10}H_{12}ON_2$ 2:2:3-Trimethylcyclohexanone semicarbazone, 1567.
 $C_{10}H_{12}ON$ Sebacic semialdoxime, 755.
 $C_{10}H_{12}IS$ Geraniolene sulphide methiodide, 1531.
 $C_{10}H_{12}ON_2$ 2:4-Diacetamido-2-methylpentane, 1398.
 $C_{10}H_{12}ON_2$ 1-Triacetyl-*d*-xylopyranosidoglyoxaline-4:5-dicarboxamide, 381.
 $C_{10}H_{12}ON$ Decan-5-one oxime, 1496.
 $C_{10}H_{12}ON$ 5:5-Dimethyl-2-(1-carbamylisopropyl)hexahydropyrimidine, 1503.
 $C_{10}H_{12}ON_2$ Base, and its salts, from 2-nitro-2-ethylpropane-1:3-diol, 927.
 $C_{10}H_{12}ON_2$ Hydroxymethyl-2:4-dinitro-4-hydroxymethyl-2-ethylhexylamine, salts, 926.
 $C_{10}H_{12}O_2Ti$ Trisdimethylthallium tartrate, 1384.
 $C_{10}H_{12}ON_2$ *N*-Methyl-*N'*-diethyl-*N*-3-methylaminopropylurea, 315.
 $C_{10}H_{12}ON_2$ Nonoxyguanidine, nitrate, 967.
 $C_{10}H_{12}OP$ Diethyl *n*-hexylphosphonate, 1466.
 $C_{10}H_{12}ON_2$ 1:10-Decamethylenedioxydiamine, dihydrochloride, 967.

$C_{10}H_{14}O_4P_2$ Tetraethyl ethylenediphosphonate, 1467.
 $C_{10}H_{18}O_2Si_2$ Pentaethyldisiloxanol, 1592.

10 IV

- $C_{10}H_6O_2NBr_2$ 1:2-Dibromo-7-nitronaphthalene, 329.
 2:4-Dibromo-1-nitronaphthalene, 128.
 $C_{10}H_6O_2NCl$ 2-Chloro-6-nitronaphthalene, 330.
 2-Chloro-7-nitronaphthalene, 330.
 6-Chloro-2-nitronaphthalene, 548.
 $C_{10}H_6O_2NBr$ 2-Bromo-7-nitronaphthalene, 330.
 $C_{10}H_6O_2NI$ 2-Iodo-6-nitronaphthalene, 330.
 2-Iodo-7-nitronaphthalene, 330.
 $C_{10}H_6O_2N_2Cl_2$ 6:7-Dichloro-4-acetoxycinnoline, 232.
 $C_{10}H_6O_2N_2Br$ 1-Bromo-7-nitro-2-naphthylamine, 329.
 $C_{10}H_6O_2NS$ Propylammonium toluene-*p*-sulphonates, 385.
 $C_{10}H_6O_2N_2Cl$ 2:4:6-Trihydroxy-5-*p*-chlorobenzeneazopyrimidine, 1248.
 $C_{10}H_6ONCl$ β -*p*-Chlorobenzoylpropionitrile, 1193.
 $C_{10}H_6ONBr$ β -*p*-Bromobenzoylpropionitrile, 1193.
 $C_{10}H_6ON_2Cl$ 4-Chloro-2-amino-5-phenoxy pyrimidine, 46.
 $C_{10}H_6ON_2Cl_2$ 2:4-Dichloro-6-*p*-anisidino-1:3:5-triazine, 158.
 $C_{10}H_6O_2N_2S$ 2-Amino-4-*o*-carboxyphenylthiazole, 1657.
 isoNitroso-2-acetonylbenzthiazole, 1621.
 $C_{10}H_6ONS$ 2-Acetonylbenzthiazole, 1621.
 $C_{10}H_6ON_2Cl$ 2-Chloro-3:4:2':3':-pyridoacridone, 680.
 $C_{10}H_6ON_2Cl$ 2-*p*-Chloroanilino-4-hydroxy-6-methyl-1:3:5-triazine, 158.
 $C_{10}H_6O_2NS$ 3-Keto-2-acetyl-2:3-dihydrobenzthiazine, 1621.
 $C_{10}H_6O_2N_2S$ 2-*p*-Nitrobenzenesulphenamido-5-methylthiazole, 114.
p-Nitrophenyl 2-amino-4-methyl-5-thiazyl sulphide, 115.
 $C_{10}H_6O_2NS$ 2-Keto-1-propionyl-1:2-dihydrobenziso-thiazole *S*-oxide, 763.
 $C_{10}H_6O_2N_2Cl$ 4-Chloro-2-nitro-3-acetamidoacetophenone, 231.
 4-Chloro-2-nitro-5-acetamidoacetophenone, 231.
 $C_{10}H_6O_2N_2S$ 2-Amino-4-(*p*-nitrophenylsulphonylmethyl)thiazole, 117.
p-Nitrophenyl 2-amino-4-methyl-5-thiazyl sulphone, 117.
 $C_{10}H_6N_2ClS$ 2-*p*-Chlorobenzenesulphenamido-4-methylthiazole, 116.
p-Chlorophenyl 2-amino-4-methyl-5-thiazyl sulphide, 116.
 $C_{10}H_6O_2NCl$ 4-Chloro-2-acetamidoacetophenone, 235.
 4-Chloro-3-acetamidoacetophenone, 231.
 $C_{10}H_6O_2N_2S$ *p*-Tolyl 2-amino-5-thiazyl sulphone, 114.
 $C_{10}H_6ONClS$ 5-Chloro-3-ethyl-2-methylenebisthiazoline, 956.
 $C_{10}H_6ON_2Cl$ 7-Chloro-4-methylcinnoline methiodide, 811.
 $C_{10}H_6ONCl$ β -Benzoylpropiochloroimide, 1194.
 $C_{10}H_6ONS$ 2-Ethylidihydro-1:3-benzthiazine-4-one, 764.
 $C_{10}H_6O_2N_2S$ 2-Amino-4-(*p*-aminophenylsulphonylmethyl)thiazole, 117.
 $C_{10}H_6O_2S_2As$ 2-(*p*-Carboxyphenyl)-4-hydroxymethyl-1:3-dithia-2-arsacyclopentane, and its brucine salt, 595.
 $C_{10}H_{12}ON_2S$ α -Benzamidothiopropionamide, 1375.
 β -Benzamidothiopropionamide, 1376.
 $C_{10}H_{12}ON_2Br$ 3-Bromo-4-methylacetophenone semicarbazone, 230.
 $C_{10}H_{12}O_2NCl$ 2-Chloroethyl *N*-benzylcarbamate, 179.
 $C_{10}H_{12}O_2NI$ 2-Iodoethyl *N*-benzylcarbamate, 179.
 $C_{10}H_{12}O_2N_2S$ 2-(4'-Methylsulphonylphenyl)dihydroglyoxaline, and its toluene-*p*-sulphonate, 500.
 $C_{10}H_{12}O_2ClAs$ Phenyl-3-carboxy-*n*-propylchloroarsine, 623.
 $C_{10}H_{12}ON_2S$ 2-(4'-Sulphophenyl)-3:4:5:6-tetrahydropyrimidine, 500.
 $C_{10}H_{12}O_2N_2S$ β -Methylthiopropaldehyde dinitrophenylhydrazon, 1611.
 $C_{10}H_{12}O_2N_2Cl$ 2-Chloro-5-dimethylaminophenol *N*-methylurethane, salts, 190.
 $C_{10}H_{12}O_2N_2S$ 2-(4'-Sulphamidobenzyl)dihydroglyoxaline, and its salts, 500.
 $C_{10}H_{12}O_2N_2S$ Acetylulphanilamidoacetamide, 1375.
 $C_{10}H_{12}O_2N_2S$ 1-Acetyl-5:5-cyclopentamethylene-2-thiohydantoin, 686.
N-Dimethyl-*p*-aminodiphenyl methyl sulphone, salts, 392, 393.
N-Ethyl-*p*-methylsulphonylbenzamidine, salts, 1112.
 $C_{10}H_{12}O_2N_2S$ 2-*p*-Aminobenzenesulphonamidotetrahydropyrimidine, 822.
 $C_{10}H_{12}O_2N_2S$ β -*p*-Acetamidobenzenesulphonyl- α -methylguanidine, 821.
 Acetylulphanilamidoacetamide, hydrochloride, 1375.
 $C_{10}H_{12}OIS$ Dimethyl-2-phenoxyethylsulphonium iodide, 770.
 $C_{10}H_{12}O_2N_2S$ 5-Sulphanilamido-2-benzylthiazole, 1597.
 $C_{10}H_{12}O_2N_2P$ Adenosine diphosphate, acridine salt, 651.
 $C_{10}H_{12}ON_2I$ 4-Ureidophenyltrimethylammonium iodide, 185.
 $C_{10}H_{12}O_2N_2S$ β -Sulphanilyl- α -2-methoxyethylguanidine, 821.
 $C_{10}H_{12}ON_2S$ 4-2'-Hydroxyethylimino-5:5-cyclopentamethylene-2-thiohydantoin, 686.
 $C_{10}H_{12}O_2N_2Cl_2$ *NN'*-Diisopropylethylenediamine-*NN'*-dicarboxychloride, 315.
 $C_{10}H_{12}O_2NCl$ 9-Chlorononyl carbamate, 179.
 $C_{10}H_{12}O_2NBr$ 2-(2-Bromopropionamido)propaldehyde diethylacetal, 372.
 $C_{10}H_{12}O_2N_2S$ 3:3'-Dinitro-3:3'-dimethyldibutyl sulphone, 1517.
 $C_{10}H_{12}O_2NS$ Tris-(2-methylsulphonylethyl)nitromethane, 1516.
 $C_{10}H_{12}O_2N_2Cl$ Trimethyl-6-hydroxyhexylammonium chloride urethane, 180.
 $C_{10}H_{12}O_2NS$ Tris-(2-methylsulphonylethyl)methylamine, 1516.
 $C_{10}H_{12}O_2N_2S$ 3:3'-Diamino-3:3'-dimethyldibutyl sulphone, hydrochloride, 1517.
 $C_{10}H_{12}O_2ClSi_2$ Pentaethylchlorodisiloxane, 1592.

10 V

- $C_{10}H_9ON_2S_2$ *p*-Chlorophenyl 2-amino-4-methyl-5-thiazyl sulphone, 117.
 $C_{10}H_{11}O_2N_2S_2$ Methyl 3-nitro-3-*p*-bromophenylpropyl sulphone, 1517.
 $C_{10}H_{11}O_2N_2S_2$ 2-(4'-Methylsulphonylphenyl)dihydroglyoxalium chloride, 502.
 $C_{10}H_{13}ONH_2S_2$ 2-(2-Bromopropionamido)propaldehyde diethylmercaptal, 372.

 C_{11} Group.

- $C_{11}H_{13}$ 1-(*o*-, *m*-, and *p*-Tolyl)buta-1:3-dienes, 1094.

11 II

- $C_{11}H_8O_2$ 5-Methoxy-1:4-naphthaquinone, 354.
 $C_{11}H_{10}O$ 5-Phenylpent-2-en-4-yn-1-ol, 1585.
 $C_{11}H_{10}O_2$ 5-Methoxy-1:4-dihydroxynaphthalene, 354.
 $C_{11}H_{12}O_2$ *p*-Anisylbutadiene, 1096.
 $C_{11}H_{12}O_4$ β -3-Methoxybenzoylpropionic acid, 1194.
 $C_{11}H_{12}N_2$ 5- and 7-Dimethylaminoquinolines, and their salts, 441, 443.
 $C_{11}H_{14}O$ *o*-Methylstyrylmethylcarbinol, 1094.
m-Methylstyrylmethylcarbinol, 1094.
p-Methylstyrylmethylcarbinol, 1094.
o-Tolylpropenylcarbinol, 1094.
m-Tolylpropenylcarbinol, 1094.
p-Tolylpropenylcarbinol, 1094.
 $C_{11}H_{14}O_2$ *p*-Anisylpropenylcarbinol, 1096.
2-Methoxy-3:5-dimethylacetophenone, 538.
p-Methoxystyrylmethylcarbinol, 1096.
 $C_{11}H_{14}O_2$ Clavatul methyl ether, 612.
 β -*o*-Methoxymethylphenylpropionic acid, 1640.
 $C_{11}H_{14}O_2$ *cyclo*Hexyl aconate, 1178.
 $C_{11}H_{14}N_2$ 1-Phenyl-2:7-diazacycloheptene, and its salts, 500.
 $C_{11}H_{16}N_2$ γ -Phenylallyldimethylamine, and its salts, 168.
 $C_{11}H_{16}O$ (+) + *dl*-1:1-Dimethyl-2-phenylpropan-1-ol, 437.
 $C_{11}H_{16}O_2$ β -3:4-Dimethoxyphenylisopropyl alcohol, 127.
 $C_{11}H_{16}N_2$ *NN*-Diethylbenzamidine, salts, 1113.
NN'-Diethylbenzamidine, and its picrate, 385.
N-Methyl-*N*'-propylbenzamidines, salts, 385.
 $C_{11}H_{16}O_2$ Ethyl 2:4:4-trimethylcyclopentanone-2-carboxylate, 1029.
 $C_{11}H_{16}O_7$ 3:4-Acetone α -methyl-D-galacturonoside methyl ester, 1340.
 $C_{11}H_{16}N_2$ *NN*-Dimethyl-*N*'-ethylbenzamidine, salts, 385.
 $C_{11}H_{20}O_2$ 6-Methyl 3:4-acetone β -methylgalactoside, 1677.
 $C_{11}H_{20}N_4$ 1:5-Bis-(2'-dihydroglyoxaliny)pentane, and its toluene-*p*-sulphonate, 500.
 $C_{11}H_{21}N$ 1-Diethylaminohept-2-yne, and its picrate, 1578.
 $C_{11}H_{21}N_2$ 2-Amino-4- β -diethylaminoethylamino-5-methylpyrimidine, and its dipicrate, 45.
4-Amino-2- γ -dimethylaminopropylamino-5:6-dimethylpyrimidine, tartrate, 49.
 $C_{11}H_{21}N_2$ 10-Aminodecyl cyanide, 1371.
 $C_{11}H_{21}N_2$ 2:6-Diamino-4- β -diethylaminoethylamino-5-methylpyrimidine, 47.
2:6-Diamino-4- γ -diethylaminopropylaminopyrimidine, and its dipicrate, 47.
 $C_{11}H_{21}S$ *cyclo*Hexyl isomyl sulphide, 40.
 $C_{11}H_{21}N$ *iso*Amyl-*n*-hexylamine, oxalate, 200.

11 III

- $C_{11}H_8O_2N_4$ 8-Nitro-2:4-dihydroxy-1:3-diaza-acridine, 734
 $C_{11}H_8O_2N_4$ 5-(2:4-Dinitrobenzylidene)barbituric acid, 734.
 $C_{11}H_8NBr$ 6-Bromo-2-cyanonaphthalene, 162.
 $C_{11}H_8ON$ 6-Hydroxy-2-cyanonaphthalene, 162.
 $C_{11}H_8O_2N_4$ 2:4-Dihydroxy-1:3-diaza-acridine, and its acetate, 733.
 $C_{11}H_8N_2Cl_2$ 4:6-Dichloro-5-*p*-chlorobenzeneazo-2-methylpyrimidine, 1247.
 $C_{11}H_8ON_4$ 2-Amino-4-hydroxy-1:3-diaza-acridine, and its hydrochloride, 733.
4-Amino-2-keto-3:12-diaza-2:12-dihydroacridine, and its hydrochloride, 733.
 $C_{11}H_8O_2N_4$ 2:4-Dinitro-5-methoxy-1-naphthol, 352.
2:8-Dinitro-5-methoxy-1-naphthol, 352.
6:8-Dinitro-5-methoxy-1-naphthol, 353.
 $C_{11}H_8N_2Cl_2$ 4:6-Dichloro-5-phenyl-2-methylpyrimidine, 1361.
 $C_{11}H_8O_2N_4$ 5-Methoxy-1:4-naphthaquinone oxime, 354.
5-Methoxyquinoline-8-carboxylic acid, 440.
 $C_{11}H_8O_2N_4$ 2-(*p*-Nitrophenyl)-6-methyl-3-pyridazone, 553.
 $C_{11}H_8O_2Cl_2$ 4:6-Dichloro-2-*N*-methylanilinopyrimidine, 1247.
 $C_{11}H_8O_2N_4$ 8-Nitro-5-methoxy-1-naphthol, 352.
 $C_{11}H_8O_2N_4$ 7-Dinitro-2-acetonaphthalide, 1060.
2:4-Dinitro-5-methoxy-1-naphthylamine, 355.
 $C_{11}H_8NCl_2$ 2:4-Dichloro-3-ethylquinoline, 909.
 $C_{11}H_8N_2Cl_2$ Dichloromethylanilinopyrimidine, 1247.
 $C_{11}H_{10}O_2N_4$ 8-Hydroxyquinoline *N*-methylurethane, salts, 190.
 $C_{11}H_{10}O_2N_4$ 4-Amino-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone, 553.
 $C_{11}H_{11}ON$ β -*p*-Toluypropionitrile, 1193.

- $C_{11}H_{11}ON$, 4-Amino-2-phenyl-6-methyl-3-pyridazone, and its hydrochloride, 552.
 $C_{11}H_{11}O_2N$, β -3- and 4-Methoxybenzoylpropionitriles, 1193, 1194.
 $C_{11}H_{11}O_2N$, 2-*N*-Methylanilino-4:6-dihydroxypyrimidine, 1247.
 $C_{11}H_{11}O_2N$, 2-(*p*-Nitrophenyl)-6-methyl-3-pyridazinone, 552.
 $C_{11}H_{11}O_2N$, Acetyl-6-nitro-1-hydrindenol, 95.
 $C_{11}H_{11}O_2N$, β -Acetylacrylic acid *p*-nitrophenylhydrazone, 553.
 $C_{11}H_{11}O_2N$, 3-Keto-*n*-butyl cyanide 2:4-dinitrophenylhydrazone, 1507.
 $C_{11}H_{11}NS$, 2-Ethylthio-4-phenylthiazole, and its hydrobromide, 1658.
 $C_{11}H_{11}N_2S$, 2-Phenyl-4-cyanomethyl-1:3-dithiolan, 594.
 $C_{11}H_{11}N_2Cl$, 2-Amino-4-*p*-chloroanilino-6-methylpyrimidine, 1357.
 $C_{11}H_{11}N_2Cl$, 4-Amino-2-*p*-chloroanilino-6-methylpyrimidine, 1357.
 $C_{11}H_{11}N_2Cl$, 4-Amino-6-*p*-chloroanilino-2-methylpyrimidine, 1358.
 $C_{11}H_{11}N_2Cl$, 4-Chloro-2-amino-6-*p*-toluidinopyrimidine, and its hydrochloride, 1362.
 $C_{11}H_{11}ON$, 3-Benzamidopropyl cyanide, 1370.
 $C_{11}H_{11}O_2N$, 3-Nitro-1-phenyl-2-methylpropyl cyanide, 1505.
 $C_{11}H_{11}O_2N$, 2-(5-Nitro-2-acetamidophenyl)propylene, 810.
 $C_{11}H_{11}O_2N$, 2-Nitro-5-acetamido-4-methylacetophenone, 230.
 $C_{11}H_{11}O_2N$, 3-Nitro-5-acetamido-4-methylacetophenone, 229.
 $C_{11}H_{11}N_2S$, 5-Benzyl-6-methyl-2:4-dithiohydantoin, 683.
 $C_{11}H_{11}N_2S$, 2-*p*-Toluenesulphenamido-4-methylthiazole, 116.
 $C_{11}H_{11}N_2S$, *p*-Tolyl 2-amino-4-methyl-5-thiazyl sulphide, 116.
 $C_{11}H_{11}O_2N$, 3-Acetamido-4-methylacetophenone, 229.
 $C_{11}H_{11}O_2N$, 7-Methoxy-1-tetralone oxime, 196.
 $C_{11}H_{11}O_2N$, Methyl β -benzoylpropimino-ether, hydrochloride, 1195.
 $C_{11}H_{11}O_2N$, β -4-Methoxybenzoylpropionamide, 1195.
 $C_{11}H_{11}O_2N$, α -Amidino- α -vanillylideneacetamide, hydrochloride, 617.
 $C_{11}H_{11}O_2N$, β -Carbamylisobutaldehyde 2:4-dinitrophenylhydrazone, 1503.
 $C_{11}H_{11}N_2I$, 4-Methylcinoline ethiodide, 811.
 $C_{11}H_{11}OS$, β -Benzylthio-*n*-butaldehyde, 1611.
 $C_{11}H_{11}O_2N$, Benzamidoacetiminoether, hydrochloride, 1374.
 $C_{11}H_{11}O_2N$, 2-(3':4'-Dimethoxyphenyl)dihydroglyoxaline, and its picrate, 500.
 $C_{11}H_{11}O_2N$, *N*-(2-Nitroethyl)-1:2:3:4-tetrahydroquinoline, hydrochloride, 1488.
 $C_{11}H_{11}O_2N$, 2-*iso*Propylideneamino-4-methoxybenzamide, 894.
 $C_{11}H_{11}N_2S$, α -Amino- γ -benzylthio-*n*-butyronitrile, hydrochloride, 1611.
 $C_{11}H_{11}ON$, 6-Methoxy-2-methyltetrahydroisquinoline, picrate, 193.
 $C_{11}H_{11}O_2N$, *o*-Acetamidophenyldimethylcarbinol, 810.
 $C_{11}H_{11}O_2N$, *O*'-Butyl benzhydroxamate, 968.
 $C_{11}H_{11}O_2N$, β -Dimethylamino-3- and -4-hydroxypropiophenones, hydrochlorides, 1192.
 $C_{11}H_{11}O_2N$, β -3-Methoxyphenylbutyramide, 196.
 $C_{11}H_{11}O_2N$, *p*-Methoxyphenylpropaldehyde semicarbazone, 1572.
 $C_{11}H_{11}O_2N$, *O*-Acetylhomovanillylamine, hydrochloride, 616.
 $C_{11}H_{11}O_2N$, α -Amino- γ -(*p*-methoxyphenyl)butyric acid, 1572.
 $C_{11}H_{11}O_2N$, 5-Nitromethyldihydroeugenol, 126.
 $C_{11}H_{11}O_2N$, 9-*d*-Mannopyranosidoadenine, and its picrate, 357.
 $C_{11}H_{11}ON$, 3-Acetamido-5-dimethylaminotoluene, 187.
 $C_{11}H_{11}O_2N$, Acetyl-5-dimethylamino-*m*-cresol, 188.
 $C_{11}H_{11}O_2N$, 4-Dimethylaminobenzyl alcohol *N*-methylurethane, methiodide, 190.
 $C_{11}H_{11}O_2N$, 4-Dimethylamino-*o*-cresol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{11}O_2N$, 5-Dimethylamino-*m*-cresol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{11}O_2N$, 2-Dimethylamino-*p*-cresol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{11}O_2N$, Ethyl-2-nitropropylanilines, hydrochlorides, 1489.
 $C_{11}H_{11}O_2N$, 2-Nitro-4-dimethylamino-1-*iso*propylbenzene, methiodide, 187.
 $C_{11}H_{11}O_2N$, Ethyl 2-methyliminazole-4-carboxylate-1-acetate, 102.
 $C_{11}H_{11}O_2S$, 4:5-Dimethoxy-2-*n*-propylbenzenesulphonic acid, salts, 126.
 $C_{11}H_{11}O_2S$, *O*-Methyldihydroeugenol-5-sulphonic acid, and its salts, 126.
 $C_{11}H_{11}O_2N_4$, 1-*d*-Glucosidoglyoxaline-4:5-dicarboxamide, and its hydrate, 380.
 $C_{11}H_{11}NCl$, Ethyl 3-chloropropylaniline, 311.
 $C_{11}H_{11}ON$, 1-Amino-7-methoxytetralin, hydrochloride, 196.
 $C_{11}H_{11}ON$, 4-Diethylamino-*o*-cresol, and its methiodide, 188.
 $C_{11}H_{11}ON$, 3-Dimethylamino-4-*iso*propylphenol, and its methiodide, 188.
 $C_{11}H_{11}ON$, 5-Dimethylamino-2-*iso*propylphenol, and its methiodide, 188.
 $C_{11}H_{11}ON$, Dimethyl- α -(hydroxyphenyl)-*n*-propylamines, and their salts, 194.
 $C_{11}H_{11}ON$, Dimethyl- α -(4-hydroxy-*m*-tolyl)ethylamine, hydrochloride, 194.
 $C_{11}H_{11}ON$, Dimethyl- β -(3-methoxyphenyl)ethylamine, salts, 193.
 $C_{11}H_{11}ON$, Ethyl-3-hydroxypropylaniline, 311.
 $C_{11}H_{11}ON$, γ -(3- and -4-Methoxyphenyl)- α -methyl-*n*-propylamines, salts, 196.
 $C_{11}H_{11}ON$, Methyl-2-ethoxyethylaniline, 311.
 $C_{11}H_{11}O_2N$, 5-Aminomethyldihydroeugenol, and its hydrochloride, 126.
 $C_{11}H_{11}O_2N$, 1-Dimethylamino-6-acetoxyhept-4-en-2-yne, and its methoperchlorate, 1579.
 $C_{11}H_{11}O_2N$, *p*-Toluenesulphonmethyloisopropylamide, 311.
 $C_{11}H_{11}O_2N$, Ethyl α -(α -ethoxyethylideneamino)- β -acetoxyacetate, 101.
 $C_{11}H_{11}NS$, γ -Benzylthio-*n*-butylamine, and its hydrochloride, 1611.
 $C_{11}H_{11}ON$, 4-Dimethylamino-2-hydroxybenzylidimethylamine, dihydrochloride, 188.
 $C_{11}H_{11}N_2Cl$, 2:6-Dichloro-4- γ -diethylaminopropylaminopyrimidine, and its salts, 730.
 $C_{11}H_{11}ON$, 1-Diethylaminohept-4-en-2-yn-6-ol, and its picrate, 1579.
 $C_{11}H_{11}O_2N$, Ethyl α -ethoxyethylideneaminomalonate, 100.
 $C_{11}H_{11}O_2N$, Ethyl *iso*propoxycarbethoxymethyleneaminomalonate, 100.
 $C_{11}H_{11}N_2Cl$, 2-Chloro-4- β -diethylaminoethylamino-6-methylpyrimidine, and its dipicrate, 787.
 $C_{11}H_{11}N_2Cl$, 4-Chloro-6- β -diethylaminoethylamino-2-methylpyrimidine, and its dipicrate, 1356.
 $C_{11}H_{11}N_2Cl$, 4-Chloro-2- γ -dimethylaminopropylamino-5:6-dimethylpyrimidine, 48.

- $C_{11}H_{20}ON_4$ 4- β -Diethylaminoethylamino-2-hydroxy-6-methylpyrimidine, and its salts, 786.
 4- β -Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine, hydrochloride, 1356.
 $C_{11}H_{20}O_2N_4$ 2- γ -Dimethylaminopropylamino-4-hydroxy-5:6-dimethylpyrimidine, 48.
 $C_{11}H_{20}O_2N_4$ 2- γ -Diethylaminopropylamino-4:6-dihydroxypyrimidine, and its salts, 730.
 $C_{11}H_{20}O_2N_4$ 4- γ -Diethylaminopropylamino-2:6-dihydroxypyrimidine, and its salts, 731.
 $C_{11}H_{20}O_2Cl_2$ 10-Chlorodecyl chloroformate, 178.
 $C_{11}H_{20}O_2S_2$ 6-Methyl 3:4-acetone β -methylgalactoside 2-sulphate, barium salt, 1678.
 $C_{11}H_{20}NB_2$ 10-Bromodecyl cyanide, 1370.
 $C_{11}H_{20}N_2Cl$ 4-Chloro-2-amino-6- β -diethylaminoethylamino-5-methylpyrimidine, 47.
 $C_{11}H_{20}N_2Br$ 5-Bromo-2-amino-4- β -diethylaminoethylamino-6-methylpyrimidine, 46.
 $C_{11}H_{21}O_2N$ Ethyl 4-propylpiperidine-2-carboxylate, 224.
 $C_{11}H_{21}O_2N_2$ 5:7-Dinitro-3-hydroxymethyl-5:7-diethyl-1-oxa-3-azacyclooctane, and its hydrochloride, 926.
 $C_{11}H_{21}O_2N_2$ 5-Nitro-5-ethyl-3-(2-nitro-2-hydroxymethylbutyl)tetrahydro-1:3-oxazine, 926.
 $C_{11}H_{21}S$ Dihydromyrcene sulphide methiodide, 1528, 1531.
 $C_{11}H_{21}O_2S$ cycloHexyl isomethyl sulphone, 40.
 $C_{11}H_{21}S_2$ 2:2:6:6-Tetramethyltetrahydrothiopyran methiodide, 1108.
 $C_{11}H_{21}ON$ Triethyl-2-ethylaminoethylurea, 315.
 $C_{11}H_{21}O_2P$ Diethyl *n*-heptylphosphonate, 1466.

11 IV

- $C_{11}H_{10}O_2N_2Cl$ 4-Chloro-2-(*p*-nitrophenyl)-6-methyl-3-pyridazine, 553.
 $C_{11}H_{10}O_2NS$ 4-*o*-Carboxyphenyl-2-methylthiazole, 1657.
 $C_{11}H_{10}O_2NS$ 4-Phenyl-2-methylthiazole-5-carboxylic acid, 1657.
 $C_{11}H_{10}O_2N_2Cl$ 5-*p*-Chlorobenzeneazo-4:6-dihydroxy-2-methylpyrimidine, 947.
 $C_{11}H_{10}ON_2S$ 5-Acetamido-4-phenylthiazole, 1598.
 $C_{11}H_{10}ON_2S_2$ 5-Acetamido-2-mercapto-4-phenylthiazole, 1603.
 $C_{11}H_{10}ON_2Cl$ 2-Chloro-7-acetamido-4-methyl-1:8-naphthyridine, 1409.
 $C_{11}H_{10}O_2N_2S$ 5-Amino-4-carboxy-2-benzylthiazole, 1596.
 $C_{11}H_{10}O_2N_2S$ 4-*p*-Aminophenylsulphonylpyridine *N*-oxide, 54.
 $C_{11}H_{10}O_2N_2S$ 3-*p*-Nitrobenzenesulphonamido-6-methylpyridazine, 243.
 $C_{11}H_{10}ON_2Cl$ 4-Chloro-2-amino-6-*p*-anisidinopyrimidine, and its hydrochloride, 1362.
 $C_{11}H_{10}O_2NS$ *N*-Acetyl derivative of 2-methyldihydro-1:3-benzthiazine-4-one, 764.
 $C_{11}H_{10}O_2N_2S$ *N*-(*p*-Aminobenzenesulphonimido)pyridine, 65.
 $C_{11}H_{10}O_2N_2S_2$ 2-*p*-Nitrobenzenesulphenamido-4:5-dimethylthiazole, 114.
 $C_{11}H_{10}O_2NS$ 6-Methoxyquinoline-4-sulphonic acid, 1553.
 $C_{11}H_{10}ONCl$ 2-(4-Chloro-2-acetamidophenyl)propylene, 810.
 $C_{11}H_{10}O_2N_2S_2$ *p*-Tolyl 2-amino-4-methyl-5-thiazyl sulphone, 117.
 $C_{11}H_{10}O_2N_2S$ 3-Sulphanilamido-6-methylpyridazine, and its dihydrochloride, 243.
 $C_{11}H_{10}O_2N_2S$ β -Acetylthiopropaldehyde dinitrophenylhydrazine, 1610.
 $C_{11}H_{10}N_2Cl$ 6-Chloro-4-methylcinoline ethiodide, 811.
 $C_{11}H_{10}O_2N_2S_2$ 4-Methyl-2-sulphanilamidomethylthiazole, 1373.
 $C_{11}H_{10}ONBr$ 4-Bromo- β -dimethylaminopropiophenone, hydrochloride, 1193.
 $C_{11}H_{10}O_2NCl$ 5-Chloro-2-acetamidophenyldimethylcarbinol, 810.
 $C_{11}H_{10}O_2N_2S$ 2-(4'-Methylsulphonylphenyl)-3:4:5:6-tetrahydropyrimidine, and its toluene-*p*-sulphonate, 500.
 $C_{11}H_{10}O_2N_2S$ 1-(4'-Sulphophenyl)-2:7-diazacycloheptene, 500.
 $C_{11}H_{10}O_2N_2S$ β -Ethylthiopropaldehyde dinitrophenylhydrazine, 1611.
 $C_{11}H_{10}O_2IS$ Dimethyl-2-benzoyloxyethylsulphonium iodide, 769.
 $C_{11}H_{10}O_2NS$ Methyl 2-benzamidopropyl sulphone, 1479.
 $C_{11}H_{10}O_2N_2S_2$ α -Acetylsulphanilamidothiopropionamide, 1375.
 $C_{11}H_{10}O_2N_2S$ β -*p*-Acetamidobenzenesulphonyl- $\alpha\alpha$ -dimethylguanidine, 821.
 $C_{11}H_{10}O_2N_2S$ 5-Nitroso-6-amino-4-*d*-mannosidamino-2-methylthiopyrimidine, 356.
 $C_{11}H_{10}NIS$ Dimethyl-2-benzylaminoethylsulphonium iodide, 771.
 $C_{11}H_{10}ON_2S$ 4:2'-Hydroxyethylimino-5:5-(3'-methyleyclopentamethylene)-2-thiohydantoin, 686.
 $C_{11}H_{10}ON_2Cl$ 6-Chloro-4- γ -diethylaminopropylamino-2-hydroxypyrimidine, and its salts, 731.
 $C_{11}H_{10}O_2N_2S$ 3-Nitro-5-*n*-butylsulphonyl-3-methyl-*n*-amyl cyanide, 1507.
 $C_{11}H_{10}O_2NCl$ 10-Chlorodecyl carbamate, 179.
 $C_{11}H_{10}O_2N_2I$ Trimethyl-2-hydroxyethylammonium iodide piperidylcarbamate, 180.

11 V

- $C_{11}H_{10}O_2N_2ClS$ *p*-Chlorophenyl 2-acetamido-5-thiazyl sulphone, 114.
 $C_{11}H_{10}ONIS$ Dimethyl-2-benzamidomethylsulphonium iodide, 771.

 C_{12} Group.

- $C_{12}H_8$ Acenaphthylene, photochemical decomposition of, 109.

12 II

- $C_{12}H_{10}O_4$ 2-Benzofuryl β -carboxyethyl ketone, 1194.
 Benzyl aconate, 1178.
 Dimethyl octa-1:7-dien-3:5-diyne-1:8-dicarboxylate, 1589.
 $C_{12}H_{10}Cl_2$ Bischloromethylnaphthalenes, 1433.
 $C_{12}H_{11}N_2$ *N*-2-Pyridylbenzamidine, and its salts, 1115.
 $C_{12}H_{11}N_2$ 12-Amino-2:3-dihydro- β -quinidene, and its hydrochloride, 635.
 $C_{12}H_{11}N$ 1-Ethyl-2-methylene-1:2-dihydroquinoline, 956.
 1-Ethyl-4-methylene-1:4-dihydroquinoline, 956.

- $C_{12}H_{16}N_2$ 2-Amino-5-benzeneazo-4:6-dimethylpyrimidine, 51.
 $C_{12}H_{14}O_2$ Dodeca-3:9-dien-5:7-diyne-2:11-diol, 1582.
 $C_{12}H_{14}O_2$ Clavatol acetate, 612.
 $C_{12}H_{16}O_2$ *cyclo*Hexyl coumalate, 1179.
 $C_{12}H_{14}O_2$ Octa-3:5-diyne-1:8-diol diacetate, 1582.
 $C_{12}H_{14}O_2$ *O*-Carbethoxyhomovanillin, 1694.
 $C_{12}H_{14}O_2$ *O*-Carbethoxyhomovanillic acid, 1694.
 $C_{12}H_{14}Cl_2$ 5:8-Bischloromethyl-1:2:3:4-tetrahydronaphthalene, 1434.
 $C_{12}H_{14}N_2$ 2:3-Dimethyl-5-ethylindole, 1633.
 $C_{12}H_{16}P$ Phenyldiallylphosphine, 1448.
 $C_{12}H_{16}As$ Phenyldiallylarsine, 1450.
 $C_{12}H_{16}O_2$ γ -(2-Hydroxy-3:5-dimethylphenyl)butyric acid, 537.
 $C_{12}H_{16}N_2$ 1-Benzyl-2:7-diazacycloheptene, and its picrate, 500.
 NN -Pentamethylenebenzamidine, and its picrate, 392, 394.
 $C_{12}H_{16}S$ *cyclo*Hexyl phenyl sulphide, 40.
 $C_{12}H_{16}N_2$ 2:3-Dimethyl-6-ethylindoline, 1633.
 $C_{12}H_{17}N_2$ 7-Amidino-9-*p*-aminophenylphenanthridine, trihydrochloride, 86.
 $C_{12}H_{18}O_2$ *m-n*-Amyloxyanisole, 104.
 $C_{12}H_{18}O_4$ 2:5-Diallyl 1:4-3:6-dianhydromannitol, 1407.
 $C_{12}H_{18}O_4$ Diallyl dianhydrosorbitol, 1407.
 $C_{12}H_{18}N_2$ *N*-Methyl-*NN'*-diethylbenzamidine, salts, 385.
 $C_{12}H_{18}N_2$ *N*-Methyl-*N'N'*-diethylbenzamidine, salts, 385.
 $C_{12}H_{18}S$ 3:3'-Dicyclohexenyl sulphide, 1529.
 $C_{12}H_{20}O_2$ 1-*cyclo*Hexenylpentane-1-carboxylic acid, 773.
 $C_{12}H_{20}O_2$ 1-*cyclo*Hexylpent-1-ene-1-carboxylic acid, 772.
 $C_{12}H_{20}O_2$ 3:4-Acetone 2-methyl α -methyl-*n*-galacturonoside methyl ester, 1340.
 $C_{12}H_{20}N_2$ 2-Amino-6-dimethylamino-4-isopropyltoluene, 187.
 $C_{12}H_{20}N_2$ 2:5-Di-*sec*-butylpyrazine, and its chloroplatinate, 375.
 $C_{12}H_{20}S$ *cyclo*Hexyl *cyclo*hexenyl sulphide, 1529.
 $C_{12}H_{21}N_2$ 2-Amino-3:6-di-*sec*-butylpyrazine, and its salts, 376.
 $N\beta$ -Diethylaminoethylphenylenediamines, 916.
 $C_{12}H_{21}P$ Tri- β -methylallylphosphine, 1449.
 $C_{12}H_{21}As$ Tri- β -methylallylarsine, 1450.
 $C_{12}H_{22}O_2$ 1-*cyclo*Hexylpentane-1-carboxylic acid, 772.
 $C_{12}H_{22}O_2$ *l*-Menthoxycetic acid, silver salt, 511.
 $C_{12}H_{22}O_{11}$ Sucrose, conversion of, into pyridazine derivatives, 239; conversion of, into thiazole derivatives, 590; solubility of, at high temperatures, 1678.
 $C_{12}H_{22}S_4$ Dicyclohexyl tetrasulphide, 1549.
 $C_{12}H_{22}S_6$ Dicyclohexyl hexasulphide, 1550.
 $C_{12}H_{23}N_2$ 2-Amino-5- β -diethylaminoethylamino-4:6-dimethylpyrimidine, and its dipicrate, 51.
 $C_{12}H_{23}N_2$ 4-Amino-2- β -diethylaminoethylamino-5:6-dimethylpyrimidine, 48.
 $C_{12}H_{23}N_2$ 5-Amino-2- β -diethylaminoethylamino-4:6-dimethylpyrimidine, and its dipicrate, 51.
 $C_{12}H_{23}N_2$ 5-Amino-4- β -diethylaminoethylamino-2:6-dimethylpyrimidine, 50.
 $C_{12}H_{23}N_2$ 2-Amino-4- γ -diethylaminopropylamino-5-methylpyrimidine, 45.
 $C_{12}H_{24}O$ 6-Ethyldec-6-en-5-ol, 758.
 $C_{12}H_{24}N_2$ *N-cyclo*Hexyl- $\alpha\alpha$ -diethylacetamidine, hydrochloride, 1114.
 $C_{12}H_{24}N_2$ 2:6-Diamino-4- γ -diethylaminopropylamino-5-methylpyrimidine, and its bis-3:5-dinitrobenzoate, 47.
 $C_{12}H_{24}S$ Methyl*cyclo*hexyl *iso*amyl sulphide, 40.
 $C_{12}H_{24}N$ *cyclo*Hexyl-*n*-hexylamine, hydrochloride, 201.
 $C_{12}H_{24}N_2$ 2:4:4:6-Tetramethyl-2-(2-amino*isobutyl*)-2:3:4:5-tetrahydropyrimidine, 1398.
 $C_{12}H_{26}O$ *n*-Propyl-*n*-octylcarbinol, 758.
 $C_{12}H_{26}O_2$ Dodecane-2:11-diol, 1582.
 $C_{12}H_{26}O_2$ Dodecane-4:9-diol, 1582.
 $C_{12}H_{27}N$ Di-*n*-hexylamine, *m*-nitrobenzenesulphonate, 199.
 $C_{12}H_{27}N_2$ 2:4:4:6-Tetramethyl-2-(2-amino*isobutyl*)hexahydropyrimidine, 1399.
 $C_{12}H_{27}N_2$ 2-Amino-1:3-bis(diethylamino)-2-methylpropane, 1513.

12 III

- $C_{12}H_8N_2Cl_2$ 2:7-Dichloro-*p*-phenanthroline, 1661.
 $C_{12}H_8O_2N_2$ 2:4:6-Trinitro-5-acetoxy-1-naphthol, 353.
 $C_{12}H_8N_2Cl_2$ 2-Chloro-*p*-phenanthroline, 1660.
 $C_{12}H_8N_2Cl_2$ 5:4'-Dichloro-1-phenylbenzotriazole, 938.
 $C_{12}H_8ON$ 2-Hydroxy-*p*-phenanthroline, 1660.
 $C_{12}H_8ON$ *p*-Phenanthroline *N*-oxide, 1661.
 $C_{12}H_8O_2N_2$ 5:5'-Dicyano- $\alpha\beta$ -2:2'-difurylthane, 398.
 $C_{12}H_8O_2N_2$ 5:5'-Dicyanodifurfuryl ether, 397.
 $C_{12}H_8O_2N_2$ 2:4-Dinitro-5-acetoxy-1-naphthol, 353.
 $C_{12}H_8O_2N_4$ 2:4:6:8-Tetranitro-1:5-dimethoxynaphthalene, 352.
 $C_{12}H_8Cl_2S_4$ Di-*p*-chlorophenyl tetrasulphide, 1549.
 $C_{12}H_8ON$ 2-Cyano-6-methoxynaphthalene, 162.
 $C_{12}H_8O_2N$ 2-Benzofuryl β -cyanoethyl ketone, 1194.
 $C_{12}H_8O_2N$ 6-Nitro-2-naphthyl acetate, 331.
 $C_{12}H_8O_2N$ 7-Nitro-2-naphthyl acetate, 331.
 $C_{12}H_8O_2N_2$ 2:4:6-Trinitro-1:5-dimethoxynaphthalene, 353.
 $C_{12}H_8O_2N_2$ 2:4:8-Trinitro-1:5-dimethoxynaphthalene, 352.
 $C_{12}H_8O_2N_3$ 1:3:5-Tris-2':2':2'-trinitroethylbenzene, 1237.
 $C_{12}H_8N_2Cl_2$ 9:12-Dichloro-2:3-dihydro- β -quinindene, 636.

- $C_{11}H_{10}ON$, 2-Benzamidopyridine, and its salts, 388.
 $C_{11}H_{10}ON_4$, 1-Amino-2-benzamidoethylidenemalononitrile, 1375.
 $C_{11}H_{10}ON_4$, 2-Methylamino-4-hydroxy-1:3-diaza-acridine, 734.
 $C_{11}H_{10}ON_4$, 4-Guanidino-2-hydroxy-1:3-diaza-acridine, and its salts, 734.
 $C_{11}H_{10}ON_4$, 3-Hydroxypyridine *N*-phenylurethane, and its methiodide, 190.
 $C_{11}H_{10}ON_4$, 3-Phthalimidopropyl cyanide, 1370.
 $C_{11}H_{10}ON_5$, 5-Nitro-*ON*-diacetylindoxyl, 611.
 $C_{11}H_{10}ON_5$, 2:8-Dinitro-1:5-dimethoxynaphthalene, 352.
 $C_{11}H_{10}ON_5$, 2:4-Dinitro-1:5-dimethoxynaphthalene, 352.
 $C_{11}H_{10}ON_5$, 2:6-Dinitro-1:5-dimethoxynaphthalene, 353.
 $C_{11}H_{10}ON_5$, 4:8-Dinitro-1:5-dimethoxynaphthalene, 352.
 $C_{11}H_{10}ON_5$, 2:4:8-Trinitro-1-methylamino-5-methoxynaphthalene, 355.
 $C_{11}H_{10}ClAs$, Diphenylchloroarsine, action of heat on, 429.
 $C_{11}H_{11}ON$, 8-Anilino-6-hydroxy-2-methylpurine, hydrochloride, 946.
 $C_{11}H_{11}ON_2$, 3-Nitro-3'-aminodiphenylamine, 597.
 $C_{11}H_{11}ON_2$, 4-Nitro-1:5-dimethoxynaphthalene, 352.
 $C_{11}H_{11}ON_2$, Phthaldo-2-acetoxyethylimide, 530.
 $C_{11}H_{11}NCl$, 9-Chloro-12-amino-2:3-dihydro- β -quinindene, and its hydrochloride, 636.
 $C_{11}H_{11}NCl_2$, 4-Chloro-6-*p*-chloroanilino-2:5-dimethylpyrimidine, 1358.
 $C_{11}H_{11}ClSi$, Diphenylchlorosilane, 1593.
 $C_{11}H_{12}ON$, 6-Acetamido-8-methylquinoline, 681.
 $C_{11}H_{12}ON$, 8-Acetamido-7-methylquinoline, 441.
 $C_{11}H_{12}ON$, 5-Amino-2-acetamidonaphthalene, 548.
 $C_{11}H_{12}ON$, 8-Amino-2-acetnaphthalide, 548.
 $C_{11}H_{13}ON_2$, Ethyl 4-methylcinnoline-7-carboxylate, 810.
 $C_{11}H_{13}ON_2$, γ -Phthalimidothiobutyramide, 1376.
 $C_{11}H_{13}OS$, 3-Hydroxy-2-*n*-butyrylthionaphthen, 1576.
 $C_{11}H_{13}ON_2$, 8-Nitro-4-amino-1:5-dimethoxynaphthalene, 354.
 $C_{11}H_{13}N_2S$, Schiff's base, from 5-amino-2-mercapto-4-phenylthiazole, 1603.
 $C_{11}H_{13}N_2Cl_2$, 4-Chloro-2-amino-6-*p*-chloroanilino-5-ethylpyrimidine, and its hydrochloride, 1362.
 $C_{11}H_{13}ON$, 1-Dimethylamino-2-hydroxynaphthalene, 188.
 $C_{11}H_{13}ON$, 4-Amino-1:5-dimethoxynaphthalene, 354.
 $C_{11}H_{13}ON_2$, γ -Phthalimidobutyramide, hydrochloride, 1377.
 $C_{11}H_{13}ON_2$, 4-Amino-5-(*N'*-phenylcarbamide)-6-hydroxy-2-methylpyrimidine, 946.
 $C_{11}H_{13}ON_2$, *N*- β -Benzoylpropionylacetamide, 1195.
 $C_{11}H_{13}ON_2$, 2:5-Diacetylacetanilide, 1634.
 $C_{11}H_{13}ON_2$, β -3:4-Dimethoxybenzoyl propionitrile, 1194.
 $C_{11}H_{13}N_2As$, Phenylbis-2-cyanoethylarsine, and its salts, 621.
 $C_{11}H_{13}N_2Cl_2$, 2-Chloro-4-*p*-chloroanilino-6-*isopropylamino*-1:3:5-triazine, 159.
 $C_{11}H_{14}ON$, Benzamido-*tert*-butyl cyanide, 1502.
 $C_{11}H_{14}ON$, β -6-Methoxyquinolyl(4)ethylamine, dihydrochloride, 1687.
 $C_{11}H_{14}ON_2$, 4-Amino-5-(*N'*-phenylguanidino)-6-hydroxy-2-methylpyrimidine, and its salts, 946.
 $C_{11}H_{14}ON_2$, 4:8-Diamino-1:5-dimethoxynaphthalene, and its hydrochloride, 354.
 $C_{11}H_{14}ON_2$, 3-Nitro-1-phenyl-2:2-dimethylpropyl cyanide, 1505.
 $C_{11}H_{14}ON_2$, 3-Nitro-1-phenyl-2-methyl-*n*-butyl cyanide, 1504.
 $C_{11}H_{14}ON_2$, 5:5'-Diamidino- $\alpha\beta$ -2:2'-difurylthane, dihydrochloride dihydrate, 398.
 $C_{11}H_{14}ON_2$, 5:5'-Diamidinodifurfuryl ether, and its dipicrate, 397.
 $C_{11}H_{14}O_2S$, Acetylougenol sultone, 127.
 $C_{11}H_{14}N_2S$, 5- β -Phenylethyl-5-methyl-2:4-dithiohydantoin, 683.
 $C_{11}H_{14}N_2As$, *p*-Aminophenylbis-2-cyanoethylarsine, 621.
 $C_{11}H_{14}BrP$, *p*-Bromophenyldiallylphosphine, 1448.
 $C_{11}H_{14}ON$, Ethyl β -benzoylpropimino-ether, and its hydrochloride, 1194.
 $C_{11}H_{14}N_2Cl$, 2-Amino-4-*p*-chloroanilino-6-*isopropylamino*-1:3:5-triazine, hydrochloride, 159.
 $C_{11}H_{14}ClS$, *p*-Chlorophenyl cyclohexyl sulphide, 1551.
 $C_{11}H_{14}ON$, 2-Amino-3-phenyl-4:4-dimethylpyrrolone *N*-oxide, 1511.
 $C_{11}H_{14}OS$, β -Benzylthioisovaleraldehyde, 1611.
 $C_{11}H_{14}ON$, β -Benzamido- $\alpha\alpha$ -dimethylpropionamide, 1503.
 $C_{11}H_{14}ON$, 6-Hydroxy-2-methyltetrahydroisoquinoline *N*-methylurethane, salts, 195.
 $C_{11}H_{14}ON$, 7- and 8-Hydroxy-1-methyltetrahydroquinoline *N*-methylurethanes, and their salts, 190.
 $C_{11}H_{14}O_2S$, cycloHexyl phenyl sulphone, 40.
 $C_{11}H_{14}ON_2$, 2-Picramido-3-methylpentane, 1497.
 $C_{11}H_{14}ON_2$, Theophylline-7- β -*d*-ribofuranoside, 1054.
 $C_{11}H_{14}N_2S$, α -Amino- γ -benzylthio-*n*-valeronitrile, hydrochloride, 1611.
 $C_{11}H_{14}ON$, 2-Acetamido-1:4-diethylbenzene, 1633.
 $C_{11}H_{14}ON$, 1-Dimethylamino-7-hydroxytetralin, methiodide, 194.
 $C_{11}H_{14}ON$, α -Dimethylaminomethylpropionophenone, hydrochloride, 1193.
 $C_{11}H_{14}ON$, Dimethoxy-2-methyltetrahydroisoquinolines, picrates, 193.
 $C_{11}H_{14}ON$, β -Dimethylamino-3-methoxypropionophenone, hydrochloride, 1192.
 $C_{11}H_{14}ON$, 3-Methoxybenzylacetone semicarbazone, 196.
 $C_{11}H_{14}ON$, 2-Methoxy-3:5-dimethylacetophenone semicarbazone, 538.
 $C_{11}H_{14}ON$, 3-Methylarabonanilide, 1063.
 $C_{11}H_{14}O_2As$, Phenyl-5-carboxy-*n*-pentaneearsonic acid, 623.
 $C_{11}H_{14}ON$, 2-Acetamido-4-dimethylamino-1-ethylbenzene, 187.
 $C_{11}H_{14}ON$, 4-Acetamido-6-dimethylamino-*m*-xylene, 187.
 $C_{11}H_{14}ON$, 3-Diethylaminophenol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{14}ON$, 3-Dimethylamino-4-ethylphenol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{14}ON$, 5-Dimethylamino-2-ethylphenol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{14}ON$, 6-Dimethylamino-*m*-4-xylene *N*-methylurethane, and its salts, 190.
 $C_{11}H_{14}ON$, 2-Hydroxy-5-methylbenzylidimethylamine *N*-methylurethane, salts, 195.
 $C_{11}H_{14}ON$, β -(3-Hydroxyphenyl)ethylamine *N*-methylurethane, salts, 195.

- $C_{12}H_{18}O_4N_2$ 2-Methyl D-arabinose phenylhydrazone, 1343.
 2-Methyl L-arabinose phenylhydrazone, 1344.
 $C_{12}H_{18}O_4Cl_2$ Thallous sucrose, 1382.
 $C_{12}H_{18}N_2Cl_2$ 2:5-Dichloro-3:6-di-*sec.*-butylpyrazine, 1182.
 $C_{12}H_{18}ON$ 5- and 6-Dimethylamino-4-isopropyl-*o*-cresols, and their methiodides, 188.
 Dimethyl- γ -(hydroxyphenyl)- α -methyl-*n*-propylamines, 194.
 Dimethyl- β -(3-methoxyphenyl)-*n*-propylamine, salts, 193.
 $C_{12}H_{18}O_2N_2$ 1-Nitro-3- and -4- β -diethylaminoethylaminobenzenes, and their salts, 916.
 $C_{12}H_{18}O_2N_2$ 2:4- and 2:5-Tetramethyldiaminophenol *N*-methylurethanes, salts, 190.
 $C_{12}H_{18}O_2Cl$ 3-Chloro diacetone glucose, 16.
 $C_{12}H_{18}NS$ γ -Benzylthio- γ -methyl-*n*-butylamine, and its hydrochloride, 1611.
 $C_{12}H_{18}N_2Cl$ 2-Chloro-3:6-di-*sec.*-butylpyrazine, 1182.
 $C_{12}H_{18}N_2As$ Phenylbis-2-amidinoethylarsine, and its salts, 622.
 $C_{12}H_{20}ON$ 2-Hydroxy-3:6-di-*sec.*-butylpyrazine, and its hydrochloride, 376.
 $C_{12}H_{20}O_2N_2$ 2:5-Di-*sec.*-butylpyrazine di-*N*-oxide, 1184.
 $C_{12}H_{20}S_2$ 5:5'-4-Methylisopropylcyclopentamethylene-2:4-dithiohydantoin, 683.
 $C_{12}H_{20}N_2Cl$ 2:6-Dichloro-4- γ -diethylaminopropylamino-5-methylpyrimidine, and its picrate, 731.
 $C_{12}H_{20}N_2As$ *p*-Aminophenylbis-2-amidinoethylarsine, and its tripicrate, 622.
 $C_{12}H_{21}ON$ Dimethyl- α -(2-methoxyphenyl)-*n*-propylamine, picrate, 193.
 $C_{12}H_{21}OP$ Tri- β -methylallylphosphine oxide, 1449.
 $C_{12}H_{21}N_2Cl$ 4-Chloro-2- β -diethylaminoethylamino-5:6-dimethylpyrimidine, 48.
 4-Chloro-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine, and its dipicrate, 1358.
 2-Chloro-4- γ -diethylaminopropylamino-6-methylpyrimidine, 787.
 4-Chloro-6- γ -diethylaminopropylamino-2-methylpyrimidine, and its dipicrate, 1357.
 $C_{12}H_{21}ON_2$ 2- β -Diethylaminoethylamino-4-hydroxy-5:6-dimethylpyrimidine, 48.
 4- β -Diethylaminoethylamino-6-hydroxy-2:5-dimethylpyrimidine, dipicrate, 1358.
 4- γ -Diethylaminopropylamino-6-hydroxy-2-methylpyrimidine, hydrochloride, 1356.
 4- γ -Diethylaminopropylamino-2-methylthio-6-methylpyrimidine, and its dihydrochloride, 787.
 $C_{12}H_{22}OS$ Dihydromyrcene thiolacetate, 138.
 $C_{12}H_{22}O_2N_2$ 4- γ -Diethylaminopropylamino-2:6-dihydroxy-5-methylpyrimidine, and its picrolonate, 731.
 $C_{12}H_{22}O_2S$ Dihydromyrcene thioglycolic acid, 39.
 $C_{12}H_{22}N_2Cl_4$ *NNN'*-Tetra-(2-chloroethyl)piperazine, salts, 529.
 $C_{12}H_{22}N_2S$ 4- β -Diethylaminoethylamino-2-methylthio-6-methylpyrimidine, and its dipicrate, 786.
 $C_{12}H_{22}N_2Cl$ 4-Chloro-2-amino-6- γ -diethylaminopropylamino-5-methylpyrimidine, 47.
 $C_{12}H_{22}N_2Br$ 5-Bromo-2-amino-4- γ -diethylaminopropylamino-6-methylpyrimidine, 46.
 $C_{12}H_{24}O_2S$ Methylcyclohexyl *isocamyl* sulphone, 40.
 $C_{12}H_{24}O_2N_2$ Carbethoxyacet-(*N*- γ -diethylaminopropyl)amide, 730.
 $C_{12}H_{24}N_2$ *NN'*-Diethyl-*NN'*-di-(2-chloroethyl)piperazine, salts, 517.
 $C_{12}H_{24}O_2N_2$ Carbethoxyacet-(*N*- γ -diethylaminopropyl)amidine, and its picrolonate, 730.
 $C_{12}H_{24}O_2N$ Nonoxyurethane, 967.
 $C_{12}H_{26}O_2N_2$ *NNN'*-Tetra-(2-hydroxyethyl)piperazine, salts, 529.
 $C_{12}H_{27}ON$ Dodecoxyamine, hydrobromide, 967.
 $C_{12}H_{27}O_2N_2$ 2-Nitro-1:3-bis(diethylamino)-2-methylpropane, 1512.
 $C_{12}H_{27}O_2P$ Diethyl *n*-octylphosphonate, 1467.
 $C_{12}H_{27}Cl_2Sn$ Tri-*n*-butylchlorotin, 1450.
 $C_{12}H_{28}O_2N_4$ 1:10-Decamethylenedioxymdiguanidine, dinitrate, 968.

12 IV

- $C_{12}H_{10}ON_2S_2$ *p*-Tolyl 2-acetamido-5-thiazyl sulphide, 113.
 $C_{12}H_8O_2N_2Cl_4$ 2:2':6:6'-Tetrachloro-4:4'-dinitrodiphenyl, 735.
 $C_{12}H_8O_2N_2Cl_2$ 3:3'-Dichloro-4:4'-dinitrodiphenyl, 129.
 $C_{12}H_8O_2N_2S$ 4-*p*-Cyanophenylsulphonylpyridine, 54.
 $C_{12}H_8ONCl_2$ 1:4-Dichloro-2-acetamidonaphthalene, 543.
 1:5-Dichloro-2-acetamidonaphthalene, 543.
 $C_{12}H_8ClBrAs$ Phenyl-*p*-bromophenylchloroarsine, 511.
 $C_{12}H_{10}ONCl$ 5-Chloro-2-acetnaphthalide, 548.
 8-Chloro-2-acetnaphthalide, 549.
 9-Chloro-12-hydroxy-2:3-dihydro- β -quinindene, 1037.
 9-Chloro-12-keto-2:3:5-12-tetrahydro- β -quinindene, 636.
 $C_{12}H_{10}OCl_2Si_2$ Diphenyltetrachlorodisiloxane, 1592.
 $C_{12}H_{10}O_2N_2Cl$ 4-Chloro-2-acetamido-5-phenoxy pyrimidine, 46.
 $C_{12}H_{10}O_2ClAs$ Phenyl-*p*-chlorophenylarsinic acid, 509.
 $C_{12}H_{10}O_2NBr$ 5-Bromo-*ON*-diacetylindoxyl, 609.
 $C_{12}H_{10}O_2N_2S$ 2-Benzamidomethylthiazole-4-carboxylic acid, 1374.
 $C_{12}H_{10}O_2N_2S$ 4:6-Dihydroxy-3-*p*-nitrophenylthio-2-methylpyridine, 54.
 $C_{12}H_{10}O_2N_2S$ 4:6-Dihydroxy-3-*p*-nitrophenylsulphonyl-2-methylpyridine, 54.
 $C_{12}H_{10}ON_2Cl$ 1-Chloro-6-amino-2-acetamidonaphthalene, 544.
 $C_{12}H_{11}O_2N_2S$ 4-*p*-Tolylsulphonylpyridine, 54.
 $C_{12}H_{11}O_2N_2Cl$ 4-Chloro-6-*p*-nitroanilino-2:5-dimethylpyrimidine, 1359.
 $C_{12}H_{11}O_2NS$ Ethyl 2-hydroxy-4-phenylthiazole-5-carboxylate, 1658.
 $C_{12}H_{11}O_2N_2S$ 4-Nitro-5-acetamido-2-benzylthiazole, 1597.
 $C_{12}H_{11}O_2N_2S$ 2-Acetamido-4-(*p*-nitrophenylsulphonylmethyl)thiazole, 117.
 p -Nitrophenyl 2-acetamido-4-methyl-5-thiazyl sulphone, 117.
 $C_{12}H_{11}ON_2S$ 5-Acetamido-2-benzylthiazole, and its salts, 1596.
 4-Methyl-2-benzamidomethylthiazole, 1373.
 $C_{12}H_{11}ON_2S$ 5-Acetamido-2-methylthio-4-phenylthiazole, 1604.
 $C_{12}H_{11}ON_2Cl$ 4-Chloro-2-methylamino-6-benzoyloxy pyrimidine, 732.
 $C_{12}H_{11}ON_2Cl$ 2-*p*-Chloroanilino-6-acetamido-4-methyl-1:3:5-triazine, 158.
 6-Chloro-4-guanidino-2-benzoyloxy pyrimidine, and its picrate, 733.

- $C_{12}H_{13}ON_2S$ Di-(2-pyrrolylmethyl) sulphide, 1659.
 $C_{12}H_{13}ON_2S$ *p*-Tolyl 2-acetamido-5-thiazyl sulphone, 114.
 $C_{12}H_{13}N_2ClAs$ *p*-Chlorophenylbis-2-cyanoethylarsine, 621.
 $C_{12}H_{13}ON_2S$ 4-Amino-5-(*N'*-phenylthiocarbamido)-6-hydroxy-2-methylpyrimidine, 945.
 $C_{12}H_{13}ON_2Cl$ 4-Amino-5-(*N'*-*p*-chlorophenylguanidino)-6-hydroxy-2-methylpyrimidine, and its salts, 947.
 $C_{12}H_{13}ON_2N_3Br$ 3-Nitro-1-*p*-bromophenyl-2:2-dimethylpropyl cyanide, 1505.
 $C_{12}H_{13}ON_2S$ 4:4'-Diacetamidobenzenesulphonanilide, 66.
 $C_{12}H_{13}ON_2S$ 2-Sulphanilamido-4-methylthiazole-5-acetic acid, and its hydrochlorides, 591.
 $C_{12}H_{14}ON_2S$ Bis-(2-acetamido-4-thiazolylmethyl) disulphide, 325.
 $C_{12}H_{14}OClAs$ *p*-Chlorophenylbis-2-carboxyethylarsine, 623.
 $C_{12}H_{14}ON_2S$ β -Acetyl-*n*-butaldehyde dinitrophenylhydrazone, 1610.
 $C_{12}H_{14}ON_2S$ 4-Methyl-2-(1'-sulphanilamidoethyl)thiazole, 1376.
 $C_{12}H_{14}ON_2S$ 4-Methyl-2-(2'-sulphanilamidoethyl)thiazole, 1376.
 $C_{12}H_{14}OClS$ *p*-Chlorophenylcyclohexyl sulphone, 1551.
 $C_{12}H_{14}ON_2S$ 1-(4'-Methylsulphonylphenyl)-2:7-diazacycloheptene, and its salts, 500.
 $C_{12}H_{14}ON_2S$ 9-*d*-Mannopyranosido-2-methylthiohypoxanthine, 357.
 $C_{12}H_{17}ON_2S$ α -Amino- γ -benzylthio-*n*-valeric acid, 1612.
 $C_{12}H_{17}ON_2S$ 2-Nitro-4-*p*-tolylsulphonyl-2-methylbutane, 1516.
 $C_{12}H_{17}ON_2S$ 9-*d*-Mannopyranosido-2-methylthioadenine, 357.
 $C_{12}H_{18}ONAs$ Phenyltrimethyl-3-cyanopropylarsonium hydroxide, salts, 623.
 $C_{12}H_{18}ON_2S$ *N,N*-Diethyl-*p*-methylsulphonylbenzamidine, salts, 1116.
 $C_{12}H_{18}ON_2S$ β -*p*-Acetamidobenzenesulphonyl- α -2-methoxyethylguanidine, 821.
 $C_{12}H_{18}N_2ClAs$ *p*-Chlorophenylbis-2-amidinoethylarsine, and its salts, 622.
 $C_{12}H_{18}ON_2Cl$ 2-Chloro-5-hydroxy-3:6-di-*sec*.-butylpyrazine, 1183.
 $C_{12}H_{18}OCl_2S$ Dihydromyrcene trichlorothioacetate, 141.
 $C_{12}H_{18}ON_2Cl$ Trimethyl-2-hydroxyethylammonium chloride *N*-phenylurethane, 180.
 $C_{12}H_{18}ON_2S$ 6-Amino-5-thioformamido-4-*d*-mannosidamino-2-methylthiopyrimidine, 356.
 $C_{12}H_{18}ON_2S$ 6-Amino-5-formamido-4-*d*-mannosidamino-2-methylthiopyrimidine, 357.
 $C_{12}H_{20}OCl_2S$ Dihydromyrcene dichlorothiolacetate, 141.
 $C_{12}H_{20}NIS$ Benzylidimethyl-(2-methylthioethyl)ammonium iodide, 771.
 $C_{12}H_{21}OCIS$ Dihydromyrcene chlorothiolacetate, 140.
 $C_{12}H_{22}N_2Cl_2S$ *NN'*-Dimethyl-di-2-chloroethylpiperazinium dithiocyanate, 322.
 $C_{12}H_{27}ON_2Cl$ Trimethyl-8-hydroxyoctylammonium chloride urethane, 181.

12 V

- $C_{12}H_{11}ON_2ClS$ *p*-Chlorophenyl 2-acetamido-4-methyl-5-thiazyl sulphide, 116.
 $C_{12}H_{11}ON_2ClS$ Chloro-*p*-aminophenylsulphonyl-2-methylpyridine, 54.
 $C_{12}H_{11}ON_2ClS$ *p*-Chlorophenyl 2-acetamido-4-methyl-5-thiazyl sulphone, 117.

 C_{13} Group.

- $C_{13}H_{11}O$ 1:6-Diaminoacridine, 596.
 $C_{13}H_{11}O$ Benzyl coumalate, 1179.
 $C_{13}H_{11}N$ 4-Methylcarbazole, and its picrate, 1560.
 $C_{13}H_{11}N$ 1:8-Diaminoacridine, 597.
 $C_{13}H_{11}N$ 1:9-Diaminoacridine, 597, 1419.
 $C_{13}H_{12}N$ 4-*p*-Aminostyrylpyridine, 560.
 $C_{13}H_{12}N$ 2- α -Naphthylidihydroglyoxaline, and its picrate, 500.
 $C_{13}H_{12}N$ 2- β -Naphthylidihydroglyoxaline, and its salts, 500.
 $C_{13}H_{13}N$ *N*-2-Pyridyl-*N'*-methylbenzamidine, and its picrate, 388.
 $C_{13}H_{14}O$ Phenyl 1-hexynyl ketone, 1630.
 $C_{13}H_{14}O$ β -(2-Methoxy-3:5-dimethylbenzoyl)acrylic acid, 538.
 $C_{13}H_{14}N$ 5-Aminotetrahydroacridine, and its hydrochloride, 636.
 $C_{13}H_{14}N$ 5:7-Diamino-1:2:3:4-tetrahydroacridine, 636.
 $C_{13}H_{14}N$ 5:9-Diamino-1:2:3:4-tetrahydroacridine, 637.
 $C_{13}H_{15}O$ 1-Keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene, 537.
 $C_{13}H_{15}O$ 1-Keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene-2- α -propionic acid, 536.
 $C_{13}H_{17}P$ *p*-Tolylallylphosphine, 1448.
 $C_{13}H_{18}O$ 5-Methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene, 537.
 $C_{13}H_{18}O$ γ -(2-Methoxy-3:5-dimethylphenyl)butyric acid, 537.
 $C_{13}H_{18}O$ 3-Amyloxyphenoxyacetic acid, 104.
 $C_{13}H_{18}O$ 1:2:3:5-Tetra-acetyl *d*-ribofuranose, 1054.
 $C_{13}H_{18}N$ *N*-Methyl-*NN'*-pentamethylenebenzamidine, salts, 385.
 $C_{13}H_{18}S$ Methylcyclohexyl phenyl sulphides, 40.
 $C_{13}H_{20}O$ Ethyl 2-ketocyclohexylmalonate, 1163.
 $C_{13}H_{20}N$ *N*-Methyl-*N'*- α -amylbenzamidine, and its picrate, 385, 389.
 $C_{13}H_{20}N$ *NNN'*-Triethylbenzamidine, salts, 385.
 $C_{13}H_{21}N$ 2-Amino-3-phenylheptane, and its hydrochloride, 1499.
 $C_{13}H_{21}N$ Benzyl-*n*-hexylamine, hydrobromide, 200.
 $C_{13}H_{21}N$ *N*-2-Diethylaminoethylbenzamidine, and its salts, 605.
 $C_{13}H_{21}N$ Ethylisopropyl-*n*-hexylacetanitrile, 741.
 $C_{13}H_{21}N$ 4-Amino-2- γ -diethylaminopropylamino-5:6-dimethylpyrimidine, and its bis-3:5-dinitrobenzoate, 48.
 $C_{13}H_{21}N$ 5-Amino-4- γ -diethylaminopropylamino-2:6-dimethylpyrimidine, 50.
 $C_{13}H_{21}N$ 2:2'-Dipiperidinoisopropylamine, and its trihydrochloride, 1513.
 $C_{13}H_{22}N$ α -Ethyl- α -isopropyl- α -*n*-hexylacetamide, 741.
 $C_{13}H_{22}N$ 2-Amino-1:3-bis(diethylamino)-2-ethylpropane, and its tripicrate, 1513.

13 III

- $C_{15}H_9O_2N$ Hydroxy-1-azanthraquinones, 544.
 $C_{15}H_9O_2N$ 1:6-Dinitroacridone, 596.
 1:9-Dinitroacridone, 597, 1418.
 $C_{15}H_9NCl_2$ 2:4-Dichloro-7:8-benzoquinoline, 906.
 $C_{15}H_9OCl_2$ 3:3'-Dichlorobenzophenone, 953.
 $C_{15}H_9NCl$ 6'-Chloro-5:6-benzoquinoline, 544.
 $C_{15}H_9O_2N$ 2-Cyano-6-acetoxynaphthalene, 162.
 $C_{15}H_9O_2N$ 1-Nitro-8-aminoacridone, 596.
 $C_{15}H_9O_2N$ 2:2'-Dinitrodiphenylamine-6-carboxylic acid, 1418.
 6:2'-Dinitrodiphenylamine-2-carboxylic acid, 597.
 6:3'-Dinitrodiphenylamine-2-carboxylic acid, 596.
 $C_{15}H_9O_2N$ 2:4:6-Trinitro-5-acetoxy-1-methoxynaphthalene, 353.
 $C_{15}H_9N_2F$ Fluoro-5-aminoacridines, and their hydrochlorides, 761.
 $C_{15}H_9N_2Cl_2$ 3:7-Dichloro-2:8-diaminoacridine, 249.
 $C_{15}H_{10}ON$ 1-Methyl-*p*-phenanthrol-2-one, 1660.
 $C_{15}H_{10}OBr_2$ 2:2'-Dibromo-4-methyldiphenyl ether, 7.
 $C_{15}H_{10}O_2N$ 4-Cyanodiphenylamine-2-carboxylic acid, 640.
 $C_{15}H_{10}O_2N$ 2:4-Dinitro-1-acetoxy-5-methoxynaphthalene, 352.
 6:8-Dinitro-1-acetoxy-5-methoxynaphthalene, 352.
 $C_{15}H_{10}O_2N$ 2:4:5:7-Tetranitro-1:8-naphthylenediamine, 81.
 $C_{15}H_{10}NCl$ 1-Chloro-4-methylcarbazole, and its picrate, 1560.
 $C_{15}H_{10}N_2Cl_2$ *N*-Phenyl-2:4-dichlorobenzamidine, and its salts, 1115.
 $C_{15}H_{11}ON$ 1:6-Diaminoacridone, 596.
 1:8-Diaminoacridone, 596.
 1:9-Diaminoacridone, 597, 1419.
 $C_{15}H_{11}O_2N$ *p*-Amino- ω -furfurylideneacetophenone, 1420.
 $C_{15}H_{11}O_2N$ *N*-*o*-Nitrophenylbenzamidine, picrate, 1115.
 $C_{15}H_{11}O_2N$ β -6-Methoxyquinolyl(4)acrylic acid, 1686.
 $C_{15}H_{11}O_2N$ 8-Nitro-1-acetoxy-5-methoxynaphthalene, 352.
 $C_{15}H_{11}O_2N$ Acetyl-2:4-dinitro-5-methoxy-1-naphthylamine, 355.
 $C_{15}H_{11}N_2I$ *p*-Phenanthroline methiodide, 1660.
 $C_{15}H_{12}ON$ β -6-Methoxyquinolyl(4)propionitrile, 1686.
 $C_{15}H_{12}O_2N_4$ 4-Acetamido-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone, 553.
 $C_{15}H_{12}O_2N_4$ 2:4-Dinitrophenylhydrazone of ketone from ozonolysis of lactone $C_8H_{10}O_3$, 807.
 $C_{15}H_{12}N_2Cl$ 4-Chloro-2-amino-6-*p*-cyanoanilino-5-ethylpyrimidine, 1362.
 $C_{15}H_{12}ClAs$ Phenyl-*p*-tolylchloroarsine, 509.
 $C_{15}H_{12}ON$ 12-Hydroxy-9-methoxy-2:3-dihydro- β -quinindene, 1037.
 12-Keto-9-methoxy-2:3:5:12-tetrahydro- β -quinindene, 636.
 $C_{15}H_{12}O_2N$ 4-Acetamido-2-phenyl-6-methyl-3-pyridazone, 552.
 $C_{15}H_{12}O_2N$ 8-Amino-1-acetoxy-5-methoxynaphthalene, 354.
 β -6-Methoxyquinolyl(4)propionic acid, 1686.
 $C_{15}H_{12}O_2N$ Sulphanil-*O*-acetylvanillylamide, sulphate, 616.
 $C_{15}H_{12}N_2Cl$ 5-Chloro-7-amino-1:2:3:4-tetrahydroacridine, 636.
 5-Chloro-8-amino-1:2:3:4-tetrahydroacridine, 636.
 5-Chloro-9-amino-1:2:3:4-tetrahydroacridine, 637.
 2- α -Naphthyldihydroglyoxalinium chloride, 502.
 $C_{15}H_{12}N_2Cl_2$ 4-Chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine, 1360.
 $C_{15}H_{12}ON_2$ 12-Amino-9-methoxy-2:3-dihydro- β -quinindene, and its hydrochloride, 636.
 6-Amino-1:2:3:4-tetrahydroacridone, 637.
 $C_{15}H_{12}O_2N$ β -6-Methoxyquinolyl(4)propionamide, 1686.
 $C_{15}H_{12}O_2N$ 5-Methyl-2-cyclohexenone 2:4-dinitrophenylhydrazone, 1270.
 $C_{15}H_{12}O_2N$ 2-Methoxy- Δ^4 -cyclohexenone 2:4-dinitrophenylhydrazone, 105.
 $C_{15}H_{12}NCl$ 8-Chloro-5-methyl-1:2:3:4-tetrahydrocarbazole, 1560.
 $C_{15}H_{12}N_2S$ 5-Benzylideneamino-2-mercapto-4- β -methylthioethylthiazole, 1612.
 $C_{15}H_{12}ON_2$ β -6-Methoxyquinolyl(4)propionamide, salts, 1687.
 $C_{15}H_{12}O_2N$ 2-Benzfuryl β -dimethylaminoethyl ketone, hydrochloride, 1193.
 4-Hydroxy-6-methoxy-3-ethylquinaldine, 1038.
 $C_{15}H_{12}O_2N$ β -6-Methoxyquinolyl(4)propionhydrazide, 1686.
 $C_{15}H_{12}OBr$ 2-Bromo-1-keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene, 537.
 $C_{15}H_{12}O_2N$ 3-Keto-2-methyl-*n*-amyl cyanide 2:4-dinitrophenylhydrazone, 1507.
 $C_{15}H_{12}O_2N$ Mesityl oxide 2:4-dinitrophenylsemicarbazone, 1390.
 3-Methylpent-3-en-2-one 2:4-dinitrophenylsemicarbazone, 1390.
 $C_{15}H_{12}O_2N$ Ethyl acetamidoformylacetate 2:4-dinitrophenylhydrazone, 101.
 $C_{15}H_{12}ON$ 5-Benzimido-2:2-dimethylpyrrolidine, 1510.
 $C_{15}H_{12}ON$ β -6-Methoxyquinolyl(4)ethylguanidine, nitrate, 1687.
 $C_{15}H_{12}O_2N$ Ethyl β -anilino- α -acetamidocrylate, 101.
 3-Nitro-4-methoxy-4-phenyl-3-methyl-*n*-butyl cyanide, 1507.
 $C_{15}H_{12}O_2N$ 2:4-Dinitrophenylcarbonyl-2:2-dimethylpyrrolidine, 1510.
 $C_{15}H_{12}N_2S$ 3-Ethyl-2-aniloethylidenethiazolidine, 959.
 $C_{15}H_{12}OP$ *p*-Methoxyphenyldiallylphosphine, 1448.
 $C_{15}H_{12}O_2N$ Ethyl β -4-methoxybenzoylpropimino-ether, hydrochloride, 1195.
 $C_{15}H_{12}ON$ 5-Ethoxy-3-dimethylaminomethylindole, and its hydrochloride, 196.
 $C_{15}H_{12}O_2N$ 2:4-Dinitrophenylhydrazone of aldehyde C_7H_4O , 752.
 $C_{15}H_{12}O_2S$ 2-*p*-Tosyl α -methyl-*l*-arabopyranoside, 972.
 2-*p*-Tosyl β -methyl-*l*-arabopyranoside, 971.
 $C_{15}H_{12}N_2S$ α -Amino- γ -benzylthio- γ -methyl-*n*-valeronitrile, hydrochloride, 1611.
 $C_{15}H_{12}ON$ 1-Dimethylamino-7-methoxytetralin, methiodide, 193.
 $C_{15}H_{12}ON$ 5-Benzamido- α -hexoamidine, hydrochloride, 1377.

- $C_{12}H_{19}O_2N$ Valeroidine, 1330.
 $C_{12}H_{19}ON$ 2-Acetamido-4-diethylaminotoluene, 187.
 $C_{12}H_{19}ON$ 2-Acetamido-4-dimethylamino-1-isopropylbenzene, 187.
 $C_{12}H_{20}O_2N$ 4-Diethylamino-*o*-cresol *N*-methylurethane, and its methiodide, 189.
 $C_{12}H_{20}O_2N$ 3-Dimethylamino-4-isopropylphenol *N*-methylurethane, and its methiodide, 189.
 $C_{12}H_{20}O_2N$ 5-Dimethylamino-2-isopropylphenol *N*-methylurethane, and its methiodide, 189.
 $C_{12}H_{20}O_2N$ Dimethyl- α -(hydroxyphenyl)-*n*-propylamine *N*-methylurethane, salts, 195.
 $C_{12}H_{20}O_2N$ Dimethyl- β -(3-hydroxyphenyl)-*n*-propylamine *N*-methylurethane, salts, 195.
 $C_{12}H_{20}O_2N$ Dimethyl- γ -(4-hydroxyphenyl)-*n*-propylamine *N*-methylurethane, salts, 195.
 $C_{12}H_{20}O_2N$ Dimethyl- α -(4-hydroxy-*m*-tolyl)ethylamine *N*-methylurethane, salts, 195.
 $C_{12}H_{20}O_2N$ 2:5-Dimethyl *l*-arabonic acid phenylhydrazide, 1064.
 $C_{12}H_{21}ON$ Dimethyl- γ -(4-methoxyphenyl)- α -methyl-*n*-propylamine, salts, 193.
 $C_{12}H_{21}ON$ 1-Diethylamino-6-acetoxyhept-4-en-2-yne, 1579.
 $C_{12}H_{21}ON$ 4-Amino-*N*-methyl-*N*-(2'-diethylaminoethyl)phenol, salts, 188.
 $C_{12}H_{21}ON$ 1-Diethylamino-4-acetoxyhept-2-yne, and its oxalate, 1579.
 $C_{12}H_{21}NS$ 4- γ -Diethylaminopropylamino-2-methylthio-6-methylpyrimidine, and its dipicrate, 787.
 $C_{12}H_{21}IP$ Methyltri- β -methylallylphosphonium iodide, 1449.
 $C_{12}H_{21}IA$ Methyltri- β -methylallylarsonium iodide, 1450.
 $C_{12}H_{21}IS$ Dicyclohexyl sulphide methiodide, 1537.
 $C_{12}H_{25}ON$ Dodecoxyguanidine, nitrate, 967.
 $C_{12}H_{25}ON$ *N*-Methyl-*N*'-diethyl-*N*-6-methylamino-*n*-hexylurea, 315.
 $C_{12}H_{25}ON$ 2-Nitro-1:3-bis(diethylamino)-2-ethylpropane, 1513.

13 IV

- $C_{12}H_9O_2N_2Cl$ Chloronitro-1-azanthraquinones, 544.
 $C_{12}H_9O_2N_2Br$ 6-Bromonitro-1-azanthraquinones, 544.
 $C_{12}H_9O_2N_2Cl$ Chloro-1-azanthraquinones, 542, 543.
 $C_{12}H_9O_2NS$ 1-Azanthraquinonesulphonic acids, salts, 542.
 $C_{12}H_9NClF$ Chlorofluoroacridines, 761.
 $C_{12}H_9O_2NS$ *N*-*p*-Nitrophenylbenzisothiazolone, 1234.
 $C_{12}H_9O_2NS$ *N*-*p*-Nitrophenylsaccharin, 1234.
 $C_{12}H_9ONCl$ 2'-Chloro-2'-formylethylidene-1-chloro-2-naphthylamine, 543.
 $C_{12}H_9ONS$ 2-Amino-2'-carboxydiphenyl sulphide lactam, 1234.
 $C_{12}H_9ONS$ 3-Hydroxy-2-2'-pyridylthionaphthen, 1577.
 $C_{12}H_9ONS$ 4-Amino-1-hydroxythioxanthone, 1234.
 $C_{12}H_9ONS$ 4'-Hydroxy-2-methylnaphtha-1':2':4:5-thiazole-3'-aldehyde anil, 978.
 $C_{12}H_9ONS$ 2-Amino-2'-carboxydiphenyl sulphone lactam, 1234.
 $C_{12}H_9ONS$ *N*-Benzenesulphonylbenzisothiazolone, reactions of, with aromatic amines, 1229.
 $C_{12}H_{10}ONF$ Fluorodiphenylamine-2-carboxylic acids, 761.
 $C_{12}H_{10}ONBr$ Bromonitro-4-methyldiphenyl ethers, 6.
 $C_{12}H_{11}O_2N_2Cl$ 5-Chloro-9-nitro-1:2:3:4-tetrahydroacridine, 637.
 $C_{12}H_{11}O_2N_2Cl$ Pyruvic acid 1-chloro-2-naphthylhydrazono, 543.
 $C_{12}H_{11}ONS$ 4-Amino-2'-carboxydiphenyl sulphide-3-sulphonic acid, 1233.
 $C_{12}H_{13}ONCl$ 12-Chloro-9-methoxy-2:3-dihydro- β -quinindene, 636.
 $C_{12}H_{13}ONCl$ *aa*-Trichloro- β -hydroxy- γ -6-methoxyquinolyl(4)propane, 1686.
 $C_{12}H_{13}ONBr$ Bromoamino-4-methyldiphenyl ethers, 7.
 $C_{12}H_{13}ONS$ 5-*NN*-Diacetylamino-2-mercapto-4-phenylthiazole, 1604.
 $C_{12}H_{13}ONS$ 2-Benzamidomethyl-4-thiazolylacetic acid, 1374.
 $C_{12}H_{13}ONS$ 4-Methyl-2-benzamidomethylthiazole-5-carboxylic acid, 1373.
 $C_{12}H_{13}ONS$ 4-*p*-Acetamidophenylsulphonylpyridine *N*-oxide, 54.
 $C_{12}H_{13}ONS$ *N*-2-Pyridyl-*p*-methylsulphonylbenzamidine, and its picrate, 1115.
 $C_{12}H_{13}ONS$ *N*-(*p*-Acetamidobenzenesulphonimido)pyridine, 65.
 $C_{12}H_{13}ONS$ 4-Methyl-2-(1'-benzamidoethyl)thiazole, 1375.
 $C_{12}H_{13}ONS$ 4-Methyl-2-(2'-benzamidoethyl)thiazole, 1376.
 $C_{12}H_{13}ONS$ *p*-Tolyl 2-acetamido-4-methyl-5-thiazyl sulphide, 116.
 $C_{12}H_{13}ONCl$ 4-*p*-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine, 1360.
 $C_{12}H_{13}ONCl$ 4-Chloro-6-*p*-anisidino-2:5-dimethylpyrimidine, 1359.
 $C_{12}H_{13}ONCl$ 4-Chloro-2-dimethylamino-6-benzoyloxy pyrimidine, 732.
 $C_{12}H_{14}ONS$ 5-Amino-4-carbethoxy-2-benzylthiazole, and its hydrochloride, 1596.
 $C_{12}H_{14}ONS$ *p*-Tolyl 2-acetamido-4-methyl-5-thiazyl sulphone, 117.
 $C_{12}H_{14}ONS$ 3-*N*-Acetylsulphanilamido-6-methylpyridazine, 243.
 $C_{12}H_{14}ONAs$ *p*-Carbamidophenylbis-2-cyanoethylarsine, 621.
 $C_{12}H_{14}ONS$ 4-Methyl-2-acetylsulphanilamidomethylthiazole, 1373.
 $C_{12}H_{14}ONS$ 2:4-Dimethyl-5-2'-aminomethylthiazole, dipicrate, 1402.
 $C_{12}H_{14}ONS$ 4:6-Dimethyl-2-sulphanilamidomethylpyrimidine, 1375.
 $C_{12}H_{14}ONS$ β -Acetylthio- β -methyl-*n*-butaldehyde dinitrophenylhydrazono, 1611.
 $C_{12}H_{14}ONS$ 4-Methyl-2-(3'-sulphanilamidopropyl)thiazole, 1377.
 $C_{12}H_{14}ONS$ 5-Benzamidothiohexoamide, 1377.
 $C_{12}H_{14}ONS$ *NN*-Pentamethylene-*p*-methylsulphonylbenzamidine, and its salts, 1116.
 $C_{12}H_{14}ONS$ α -Amino- γ -benzylthio- γ -methyl-*n*-valeric acid, 1612.
 $C_{12}H_{14}ONS$ β -*p*-Acetamidobenzenesulphonyl- α -diethylguanidine, 821.
 $C_{12}H_{14}ONS$ 2-Methyl *p*-arabinose *p*-toluenesulphonylhydrazono, 1343.
 $C_{12}H_{14}ONAs$ *p*-Carbamidophenylbis-2-amidinoethylarsine, dipicrate, 622.
 $C_{12}H_{14}ONI$ Trimethyl-2-hydroxyethylammonium iodide *N*-benzylurethane, 180.
 $C_{12}H_{14}ONI$ 5-Dimethylamino-4-isopropyl-*o*-cresol methiodide, 186.
 $C_{12}H_{14}ONS$ β -Sulphanilyl- α -2-diethylaminoethylguanidine, 821.
 $C_{12}H_{14}ONCl$ Trimethyl-9-hydroxynonylammonium chloride urethane, 181.

13 V

- $C_{12}H_9ONClS$ 5-Chloro-2-amino-2'-carboxydiphenyl sulphide lactam, 1234.
 $C_{12}H_9O_2NClS$ 5-Chloro-2-amino-2'-carboxydiphenyl sulphide, 1234.
 $C_{12}H_{15}O_2NBrS$ *iso*Butyl 3-nitro-3-*p*-bromophenylpropyl sulphone, 1517.

 C_{14} Group.

- $C_{14}H_{11}N$ 2-*p*-Amidinostyrylpyridine, dihydrochloride, 89.
 $C_{14}H_{11}N$ 5-Amino-2-cyanoacridine, 638.
 5-Amino-3-cyanoacridine, 640.
 $C_{14}H_{10}O$ Benzoic anhydride, reaction of, with aromatic compounds catalysed by boron trifluoride, 1237.
 $C_{14}H_{10}N$ 2-*p*-Cyanostyrylpyridine, 88.
 Naphthalene-1:5-diacetonitrile, 1434.
 $C_{14}H_{11}N$ 5-Amino-2-amidinoacridine, 639.
 5-Amino-3-amidinoacridine, 640.
 $C_{14}H_{11}N$ 3-Methyl-2-stilbazole, 1698.
 $C_{14}H_{11}N$ 2:7-Diamino-9-methylphenanthridine, 72.
 $C_{14}H_{11}N$ 2-(1'-Naphthylmethyl)dihydroglyoxaline, and its salts, 500.
N-Phenyl-*N'*-methylbenzamidine, salts, 389.
 $C_{14}H_{11}N$ *pp*-Bisaminomethylidiphenyl, and its dihydrochloride, 1453.
 $C_{14}H_{11}N$ 12-Amino-9-dimethylamino-2:3-dihydro- β -quinindene, and its trihydrochloride, 636.
 $C_{14}H_{11}N$ 7-Amino-2-piperidino-4-methyl-1:8-naphthyridine, 1409.
 $C_{14}H_{11}P$ *p*-Ethylphenyldiallylphosphine, 1448.
 Phenyl-di- β -methylallylphosphine, 1449.
p-Xylyldiallylphosphine, 1448.
 $C_{14}H_{10}As$ Phenyl-di- β -methylarsine, 1450.
 $C_{14}H_{10}N$ *N*-cycloHexylphenylacetamidine, and its salts, 1115.
 $C_{14}H_{12}N$ 2-Amino-4- β -diethylaminoethylaminoquinazoline, 898.
 $C_{14}H_{12}O$ 2:5-Dimethyl 1:4:3:6-dianhydromannitol, 1407.
 Dimethyl 1:4-dianhydrosorbitol, 1407.
 $C_{14}H_{12}N$ 2-Amino-4-dimethylamino-1-cyclohexylbenzene, 187.
 $C_{14}H_{12}S$ Phenyl octyl sulphide, 53.
 $C_{14}H_{12}N$ 9- β -Diethylaminoethyl-2:6:8-trimethylpurine, and its flavianate, 51.
 $C_{14}H_{12}N$ 5-Amino-3- β -diethylaminoethylamino-*o*-xylene, and its trihydrochloride, 912.
 $C_{14}H_{12}N$ 1:4-Bis-(2':7'-diazacycloheptenyl)butane, and its toluene-*p*-sulphonate, 500.
 1:8-Bis-(2'-dihydroglyoxalanyl)octane, and its toluene-*p*-sulphonate, 500.
 $C_{14}H_{12}N$ Di-*n*-hexylacetoneitrile, 741.
 Ethyl-*n*-butyl-*n*-hexylacetoneitrile, 741.
 $C_{14}H_{12}N$ 2-Amino-4- δ -diethylamino- α -methylbutylamino-6-methylpyrimidine, and its picrate, 790.
 $C_{14}H_{12}N$ *N*-cycloHexyl-1-amidino-*n*-heptane, salts, 1115.
 $C_{14}H_{12}Sn$ Di-*n*-butyldiallyltin, 1450.
 $C_{14}H_{12}N$ cycloHexyl-*n*-octylamine, hydrochloride, 201.
 $C_{14}H_{12}N$ $\alpha\alpha$ -Di-*n*-hexylacetamidine, and its picrate, 741.
 α -Ethyl- α -*n*-butyl- α -*n*-hexylacetamidine, 741.

14 III

- $C_{14}H_9N_2Cl$ 5-Chloro-2-cyanoacridine, 638.
 5-Chloro-3-cyanoacridine, 640.
 $C_{14}H_9O_2I$ 3:5-Di-iodo-2-hydroxydiphenylacetic acid, 203.
 $C_{14}H_9O_2N$ 2':4'-Dinitro-3-phenylphthalaz-4-one, 835.
 $C_{14}H_9O_2N$ 1:4-Diketo-3-(2':4'-dinitrophenyl)tetrahydrophthalazine, 837.
 Phthalyl-2':4'-dinitrophenylhydrazide, 837.
 $C_{14}H_9O_2N$ Methoxy-1-azanthraquinones, 544.
 $C_{14}H_9O_2N$ 6:7-Dihydroxy-2-methoxytetrahydroisoquinoline, salts, 195.
 $C_{14}H_9N_2I$ 1:3-Di-iodo-2-phenylpyrrocoline, hydriodide, 672.
 $C_{14}H_9NS$ Thionaphthindole, and its salts, 656.
 $C_{14}H_9N_2Cl$ 4-Chloro-2-*p*-chloroanilinoquinazoline, 780.
 $C_{14}H_9O_2N$ 3'-Cyanodiphenylamine-2-carboxylic acid, 638.
 5-Cyanodiphenylamine-2-carboxylic acid, 638.
 $C_{14}H_9O_2I$ 3:5-Di-iodo-4-hydroxydiphenylacetic acid, 203.
 $C_{14}H_9O_2N$ *o*-Carboxybenzaldehyde 2':4'-dinitrophenylhydrazide, 835.
 1:4-Dihydroxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine, 835.
 $C_{14}H_9O_2N$ *o*-Carboxybenzo-2':4'-dinitrophenylhydrazide, 837.
 $C_{14}H_9NBr$ 3-Bromo-9-methylphenanthridine, 85.
 $C_{14}H_{11}ON$ β -1- and -2-Naphthoylpropionitriles, 1194.
 $C_{14}H_{11}O_2Cl$ 4-Chlorobenzilic acid, 953.
 $C_{14}H_{11}N_2Cl$ 4-Chloro-2-(quinolylamino)-6-methylpyrimidines, 1616, 1617.
 $C_{14}H_{11}ON$ 5-Amino-2-amidoximinoacridine, 639.
 2-(Quinolylamino)-4-hydroxy-6-methylpyrimidines, 1616, 1617.
 $C_{14}H_{11}OI$ α -Phenyl- β -(3:5-di-iodo-4-hydroxyphenyl)ethane, 204.
 $C_{14}H_{11}ON$ 2:7-Diketo-1:8-dimethyl-1:2:7:8-tetrahydro-*p*-phenanthroline, 1661.
 Nitro-3-methylstilbazoles, 1698.
 $C_{14}H_{11}O_2N$ Clavatul 2:4-dinitrophenylhydrazide, 612.
 $C_{14}H_{11}ClAs$ 2-*p*-Chlorophenylisocarsindoline, and its salts, 666.
 5-Chloro-2-phenylisocarsindoline, and its salts, 668.
 $C_{14}H_{11}NS$ 3-Ethyl-2-methylene-6:7-benzbenzthiazoline, 956.
 $C_{14}H_{11}N_2I$ 2-Keto-1-methyl-1:2-dihydro-*p*-phenanthroline methiodide, 1661.
 $C_{14}H_{11}N_2S$ Azamethin[2-(4-methylthiazole)[2-(3-phenyl-4-methyl-2:3-dihydrothiazole)], 1658.

- $C_8H_{10}ON$ 12-Acetamido-2:3-dihydro- β -quinindene, 635.
 $C_8H_8O_2N$ *N*-Phenyl-*p*-methoxybenzamidine, and its hydrochloride, 396.
 $C_8H_8O_2N$ Nitro-3-methyl-2-stilbazolealkines, 1698.
 $C_8H_8O_2N$ *N*-*p*-Methoxyphenyl-*N'*-*m*-nitrophenylguanidine, 916.
 $C_8H_8O_2N$ Nitro-1:6-diacetyl-2:3-dimethylindole, 1634.
 $C_8H_8O_2N$ 8-Nitro-4-acetamido-1:5-dimethoxynaphthalene, 354.
 C_8H_8ON 4:6-Dimethyl-2-benzamidomethylpyrimidine, 1374.
 C_8H_8ON 4-(3':5'-Diacetylpenta-2':4'-dienylidene)-1:4-dihydropyridine, 1629.
 $C_{12}H_{10}O_2N$ 12-Hydroxy-9-ethoxy-2:3-dihydro- β -quinindene, 1037.
 $C_{12}H_{10}O_2N$ 6-Methoxy-2-naphthimino-ether, hydrochloride, 162.
 $C_{12}H_{10}O_2N$ 6-, 8-, and 9-Methoxy-1:2:3:4-tetrahydroacridones, 1037.
 $C_{12}H_{10}O_2N$ 4-Acetamido-1:5-dimethoxynaphthalene, 354.
 $C_{12}H_{10}O_2N$ Methyl β -6-methoxyquinolyl(4)propionate, 1686.
 $C_{12}H_{10}O_2N$ 1-Phthalimido-3-methylpentan-2-one, 375.
 $C_{12}H_{10}O_2N$ Ethyl 1-amino-2-benzamidoethylidenecyanoacetate, 1375.
 $C_{12}H_{10}O_2N$ Hepta-3:5-dien-2-one 2:4-dinitrophenylsemicarbazone, 1390.
 $C_{12}H_{10}O_2N$ 1-Methylcyclohexen-3-one 2:4-dinitrophenylsemicarbazone, 1390.
 $C_{12}H_{10}O_2N$ 4'-Chloro-3-amino-4:5-dimethyldiphenylamine, and its salts, 913.
 $C_{12}H_{10}O_2N$ 12-Chloro-9-dimethylamino-2:3-dihydro- β -quinindene, 636.
 $C_{12}H_{10}O_2N$ 2-(1'-Naphthylmethyl)dihydroglyoxalinium chloride, 502.
 $C_{12}H_{10}O_2N$ 6-*N*-Methylanilino-8-methylthio-2-methylpurine, hydrochloride, 947.
 $C_{12}H_{10}O_2N$ Benzylchlorosilane, 1693.
 $C_{12}H_{10}O_2N$ *pp'*-Bisaminomethylidiphenyl ether, 1454.
 $C_{12}H_{10}O_2N$ 9-Dimethylamino-12-keto-2:3:5:12-tetrahydro- β -quinindene, 636.
 $C_{12}H_{10}O_2N$ *N*-*p*-Methoxyphenyl-*N'*-*m*-aminophenylguanidine, hydrochloride, 916.
 $C_{12}H_{10}O_2N$ 1-Dimethylamino-2-naphthol *N*-methylurethane, 190.
 $C_{12}H_{10}O_2N$ 3-Nitro-2-hydroxy-1:6-diacetyl-2:3-dimethylindoline, 1634.
 $C_{12}H_{10}O_2N$ 1-*cis*- and -*trans*-3-Methylcyclohexyl 3:5-dinitrobenzoates, 206, 207.
 $C_{12}H_{10}O_2N$ 2-Ketocyclohexylacetic acid 2:4-dinitrophenylhydrazones, 1164.
 $C_{12}H_{10}O_2N$ 4-Methyl-3-ethyl-2-aniloehtylidene- Δ^4 -thiazoline, 959.
 $C_{12}H_{10}O_2N$ 8-Dimethylamino-4-methylcoumarin, and its methiodide, 186.
 $C_{12}H_{10}O_2N$ 4-*p*-Anisidino-6-hydroxy-2-methyl-5-ethylpyrimidine, 1361.
 $C_{12}H_{10}O_2Cl$ 3-Chloro-4:6-benzylidene α -methylglucoside, 15.
 $C_{12}H_{10}O_2Br$ 3-Bromo-4:6-benzylidene α -methylglucoside, 17.
 $C_{12}H_{10}O_2N$ 1:4-Dihydroxy-3-(2':4'-diaminophenyl)-3:4-dihydrophthalazine dihydrate, 834.
 $C_{12}H_{10}O_2N$ Dimethylcyclohexanone 2:4-dinitrophenylhydrazones, 1647.
 $C_{12}H_{10}O_2N$ Methyl 2-nitro-1:2-dimethylpropyl ketoxime *p*-nitrophenylurethane, 1491.
 $C_{12}H_{10}O_2S$ 4:6-Benzylidene α -methylglucoside sulphate, barium salt, 1677.
 $C_{12}H_{10}O_2S$ 5-Amino-2-mercapto-4- β -benzylthioisobutylthiazole, 1612.
 $C_{12}H_{10}O_2N$ 2-*p*-Chloroanilino-6-diethylamino-4-methyl-1:3:5-triazine, 158.
 $C_{12}H_{10}O_2N$ *p*-Bromophenyl-di- β -methylallylphosphine, 1449.
 $C_{12}H_{10}O_2N$ *d-trans*-3-Methylcyclohexylphenylurethane, 208.
 $C_{12}H_{10}O_2N$ 1-Keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene semicarbazone, 537.
 $C_{12}H_{10}O_2N$ 5:6-Dihydroxy-2-methyltetrahydroisooquinoline *N*-methylurethane, and its salts, 195.
 $C_{12}H_{10}O_2As$ Phenylbis-3-carboxy-*n*-propylarsine, and its disilver salt, 623.
 $C_{12}H_{10}O_2As$ Phenylbis-3-carboxy-*n*-propylarsine oxide, 623.
 $C_{12}H_{10}O_2N$ Heptoxy-3:5-dinitrobenzamide, 967.
 $C_{12}H_{10}O_2Cl$ 2-Amino-4-*p*-chloroanilino-6-dimethylaminoethylaminopyrimidine, 1363.
 $C_{12}H_{10}O_2N$ *N*-cycloHexylanisamidine, and its salts, 1115.
 $C_{12}H_{10}O_2N$ Bisacetamido-1:4-diethylbenzene, 1633.
 $C_{12}H_{10}O_2N$ 2-Hydroxycyclohexylacetic acid lactone phenylhydrazide, 1164.
 $C_{12}H_{10}O_2N$ 1-Methylamino-7-hydroxytetralin, salts, 195.
 $C_{12}H_{10}O_2N$ 2-Nitro-4-dimethylamino-1-cyclohexylbenzene, and its methiodide, 187.
 $C_{12}H_{10}O_2N$ *n*-Propyl *n*-butyl ketone 2:4-dinitrophenylhydrazones, 752.
 $C_{12}H_{10}O_2N$ 4-Picrylamino-3:3-dimethylhexane, 1497.
 $C_{12}H_{10}O_2N$ Ethyl 5-keto-2-methyl-4:5-dihydroiminazole-4-carboxylate-1-malonate, 100.
 $C_{12}H_{10}O_2N$ Phenyl dimethyl-5-cyano-*n*-pentylarsonium hydroxide, picrate, 623.
 $C_{12}H_{10}ON$ 5-Dimethylamino-2-cyclohexylphenol, 188.
 $C_{12}H_{10}ON$ Acetyl-5-dimethylamino-4-isopropyl-*o*-cresol, 186.
 $C_{12}H_{10}ON$ 2:6-Dimethyl galactose anilide, 1625.
 $C_{12}H_{10}ON$ *O*-Heptylbenzamidoxime, 968.
 $C_{12}H_{10}ON$ 5-Dimethylamino-4-isopropyl-*o*-cresol *N*-methylurethane, and its methiodide, 190.
 $C_{12}H_{10}ON$ 6-Dimethylamino-4-isopropyl-*o*-cresol *N*-methylurethane, and its methiodide, 190.
 $C_{12}H_{10}ON$ Dimethyl- γ -(3- and 4-hydroxyphenyl)- α -methyl-*n*-propylamine *N*-methylurethanes, salts, 195.
 $C_{12}H_{10}O_2S$ Phenyl octyl sulphone, 53.
 $C_{12}H_{10}O_2N$ Di-(2-ethoxyethyl)aniline, 311.
 $C_{12}H_{10}O_2N$ 5-Nitro-3- β -diethylaminoethylamino-*o*-xylene, and its salts, 912.
 $C_{12}H_{10}O_2N$ 6- γ -Diethylaminopropylamino-8-methylthio-2-methylpurine, salts, 947.
 $C_{12}H_{10}O_2N$ 2-Chloro-4- β -diethylamino- α -methylbutylamino-6-methylpyrimidine, 788.
 $C_{12}H_{10}O_2Cl$ 4-Chloro-6- β -diethylamino- α -methylbutylamino-2-methylpyrimidine, and its dipicrate, 1357.
 $C_{12}H_{10}O_2N$ 4-Chloro-6- γ -diethylaminopropylamino-2-methyl-5-ethylpyrimidine, and its dipicrate, 1360.
 $C_{12}H_{10}ON$ 4- β -Diethylamino- α -methylbutylamino-2-hydroxy-6-methylpyrimidine, and its salts, 787.
 $C_{12}H_{10}ON$ 4- γ -Diethylaminopropylamino-6-hydroxy-2-methyl-5-ethylpyrimidine, dipicrate, 1360.
 $C_{12}H_{10}O_2S$ Dihydromyrcene bis(thioglycollic acid), 39.
 $C_{12}H_{10}O_2S$ Dihydromyrcene bisglycollyl sulphone, 39.
 $C_{12}H_{10}O_2S$ 4-Methyl-2-(ω -aminodecyl)thiazole, 1377.
 $C_{12}H_{10}ON$ 2:2'-Dipiperidinoisopropylurea, 1513.
 $C_{12}H_{10}O_2Cl$ *NN'*-Di-(2-chloroethyl)-*NN'*-di-*n*-propylpiperazine, salts, 518.
 $C_{12}H_{10}O_2S$ Bis-[2-(*N*-diethylthiocarbamate)ethyl] sulphide, 850.

14 IV

- $C_{12}H_8ON_2Cl_2$ 6:7-Dichloro-4-phenoxyinnoline, 232.
 $C_{12}H_8ON_2Cl_2$ 7:8-Dichloro-4-phenoxyinnoline, 232.
 $C_{12}H_8ON_2S$ 2-Nitrothionaphthindole, 657.
 $C_{12}H_8ON_2Cl$ 4'-Chloro-2'-nitro-3-phenylphthalaz-1-one, and its picrate, 835.
 $C_{12}H_8ONClS$ 12-Chlorothionaphthindole, and its picrate, 657.
 $C_{12}H_8ON_2S$ 2-Keto-1-benzoyl-1:2-dihydrobenzisothiazole *S*-oxide, 764.
 $C_{12}H_{10}ON_2Cl$ 2-*p*-Chloroanilino-4-hydroxyquinazoline, and its hydrochloride, 778.
 $C_{12}H_{10}ON_2S$ Thioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{12}H_{11}ONS$ 2-Amino-2'-carboxy-5-methyldiphenyl sulphide lactam, 1233.
 $C_{12}H_{11}ONS$ 2-Methylaminothioxanthone, 1233.
 $C_{12}H_{11}ONS$ 2-Phenyldihydro-1:3-benzthiazine-4-one, 764.
 $C_{12}H_{11}ONS$ *N-p*-Tolylbenzisothiazolone, 1234.
 $C_{12}H_{11}OClFe$ 2-Methyl- β -naphthopyrylium ferrichloride, 348.
 $C_{12}H_{11}O_2NS$ 2-Amino-2'-carboxy-5-methoxydiphenyl sulphide lactam, 1233.
 $C_{12}H_{11}O_2NS$ 4-Amino-1-methoxythioxanthone, 1234.
 $C_{12}H_{11}O_2NS$ 2-Amino-2'-carboxy-5-methyldiphenylsulphone, 1233.
 $C_{12}H_{11}O_2NS$ 2-Amino-2'-carboxy-5-methoxydiphenylsulphone, 1233.
 $C_{12}H_{11}O_2NBr$ 5-Bromo-*o*-tolualdehyde dinitrophenylhydrazones, 692.
 $C_{12}H_{11}N_2ClBr$ 2- and 3-Chloro-5-amino-10-methylacridinium bromides, 762.
 $C_{12}H_{11}N_2BrF$ 2-Fluoro-5-amino-10-methylacridinium bromide, 762.
 $C_{12}H_{11}N_2IF$ 3-Fluoro-5-amino-10-methylacridinium iodide, 762.
 $C_{12}H_{11}O_2NS$ 2-Amino-2'-carboxy-5-methyl diphenyl sulphide, 1233.
 $C_{12}H_{11}O_2NS$ 4-Methylamino-2'-carboxydiphenyl sulphide, 1232.
 $C_{12}H_{11}O_2NCl$ 4'-Chloro-3-nitro-4:5-dimethyldiphenylamine, 913.
 $C_{12}H_{11}O_2NS$ 2-Amino-2'-carboxy-5-methoxydiphenyl sulphide, and its perchlorate, 1233.
 $C_{12}H_{11}O_2NS$ *N*-Benzoylbenzenesulphonmethyamide, 387.
 $C_{12}H_{11}O_2NS$ 4-Methylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid, 1233.
 $C_{12}H_{11}ONCl$ 6-Chloro-7-acetyltetrahydrocarbazole, 939.
 $C_{12}H_{11}ON_2S$ 4:4'-Dimethylthioazoxybenzene, 852.
 $C_{12}H_{11}ONCl$ Phenyl- α -chloro-4-hydroxy-3-methoxybenzylamine, 617.
 $C_{12}H_{11}ON_2S$ *N*-Phenyl-*p*-aminodiphenyl methyl sulphone, 394.
 $C_{12}H_{11}O_2ClSb$ Di-*o*-anisylstibinous chloride, 1569.
 $C_{12}H_{11}O_2N_2S$ 4-*p*-Acetamidomethylphenylsulphonylpyridine, 54.
 $C_{12}H_{11}O_2N_2S$ Ethyl 2-benzamidomethylthiazole-4-carboxylate, 1374.
 $C_{12}H_{11}O_2N_2Br$ 2-Nitro-1-(*p*-bromo- α -cyanobenzyl)cyclohexane, 1505.
 $C_{12}H_{11}O_2N_2S$ 2-*N*⁴-Acetylsulphanilamido-4-methylthiazole-5-acetic acid, 591.
 $C_{12}H_{11}O_2N_2S$ Ethyl 2-*p*-nitrobenzenesulphonamido-4-methylthiazole-5-acetate, and its hydrochloride, 592.
 $C_{12}H_{11}ON_2Cl$ 4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine, 1361.
 $C_{12}H_{11}ON_2As$ *p*-Acetamidophenylbis-2-cyanoethylarsine, 621.
 $C_{12}H_{11}O_2NI$ 4-Methyl-7-carbethoxycinnoline ethiodide, 811.
 $C_{12}H_{11}O_2N_2S$ 4-Methyl-2-(1'-acetylsulphanilamidoethyl)thiazole, 1376.
 $C_{12}H_{11}O_2N_2S$ 4-Methyl-2-(2'-acetylsulphanilamidoethyl)thiazole, 1376.
 $C_{12}H_{11}O_2N_2S$ Ethyl 2-sulphanilamido-4-methylthiazole-5-acetate, and its hydrochloride, 592.
 $C_{12}H_{11}ON_2S$ 6-Nitrosotionaphthindole, 657.
 $C_{12}H_{11}ON_2Cl$ 2-*p*-Chloroanilino-4-*isopropyl*amino-6-ethoxy-1:3:5-triazine, 160.
 $C_{12}H_{11}ON_2P$ *p*-Bromophenyldi(β -dibromo- β -methylpropyl)phosphine oxide, 1449.
 $C_{12}H_{11}OBrP$ Phenyldi(β -dibromo- β -methylpropyl)phosphine oxide, 1449.
 $C_{12}H_{11}O_2NS$ 4-Carbomethoxy-2-phenyl-6:6-dimethylthiazan, 1613.
 $C_{12}H_{11}O_2N_2S$ 5-(*p*-Acetamidobenzenesulphonamido)amyl cyanide, 1370.
 $C_{12}H_{11}O_2ClAs$ Phenylbis-3-carboxy-*n*-propylarsine dichloride, 623.
 $C_{12}H_{11}O_2N_2S$ 3-Ketodibutyl sulphone 2:4-dinitrophenylhydrazones, 1516.
 $C_{12}H_{11}O_2N_2S$ *m*-Di(nitro-*tert*.-butylsulphonyl)benzene, 1479.
 $C_{12}H_{11}O_2NS$ *p*-Nitrophenyl octyl sulphide, 53.
 $C_{12}H_{11}O_2NS$ *p*-Nitrophenyl octyl sulphone, 53.
 $C_{12}H_{11}ON_2As$ *p*-Acetamidophenylbis-2-amidinoethylarsine, and its salts, 622.
 $C_{12}H_{11}O_2NS$ *p*-Aminophenyl octyl sulphone, 53.
 $C_{12}H_{11}O_2N_2I$ Trimethyl-2-hydroxyethylammonium iodide *N*-diethylurethane, 180.
 $C_{12}H_{11}O_2N_2S$ *N*-2-Diethylaminoethyl-*p*-aminodiphenyl methyl sulphone, and its salts, 505.
 $C_{12}H_{11}O_2N_2Cl$ *NN'*-Di-(2-chloroethyl)-*NN'*-di(2-methoxyethyl)piperazine, salts, 529.
 $C_{12}H_{11}O_2N_2Cl$ *NN'*-Dimethyl-*NN'*-di-2-(2-chloroethoxy)ethylpiperazines, salts, 518, 532.
 $C_{12}H_{11}O_2NS$ 3-Nitro-1:5-di-(*n*-butylsulphonyl)-3-methylpentane, 1516.
 $C_{12}H_{11}O_2N_2Cl$ Trimethyl-10-hydroxydecylammonium chloride urethane, 181.
 $C_{12}H_{11}O_2NS$ 3-Amino-1:5-di-(*n*-butylsulphonyl)-3-methylpentane, 1516.

14 V

- $C_{12}H_8O_2N_2Cl_2S$ 4:7-Dichlorothioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{12}H_8O_2N_2Cl_2S$ Chlorothioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{12}H_8O_2N_2BrS$ Benzenesulphonyl-5-bromo-*o*-toluoylhydrazide, 691.
 $C_{12}H_8O_2N_2ClS$ 2-Chloro-5-nitrobenzenesulphonvanillylamide, 615.
 $C_{12}H_8ON_2ClAs$ *p*-Chloroacetamidophenylbis-2-cyanoethylarsine, 621.

 C_{15} Group.

- $C_{15}H_{12}$ 3:4:5:6-Dibenzcyclohepta-1:3:5-triene, 748.

15 II

- $C_{11}H_{10}O$ 3:4:5:6-Dibenzcyclohepta-1:3:5-trien-7-one, 749.
 $C_{11}H_{10}O$ 9-Hydroxyanthracene-10-aldehyde, 978.
 $C_{11}H_{11}N$ 3-Cyano-9-methylphenanthridine, 85.
 $C_{11}H_{11}N$ 7-Aminoquinoline, 610.
 11-Aminoquinoline, and its hydrochloride, 610.
 $C_{11}H_{12}O$ 3:4:5:6-Dibenzcyclohepta-3:5-dien-2-one, 749.
 $C_{11}H_{12}O$ 7-Hydroxyflavylium hydroxide, salts, 349.
 $C_{11}H_{12}O$ Anhydrojavanicin, 1027.
 $C_{11}H_{12}N$ 4-Phenyl-3-methylcinnoline, picrate, 1652.
 $C_{11}H_{12}Br$ 3:4:5:6-Dibenzcyclohepta-1:3:5-triene dibromide, 748.
 $C_{11}H_{12}N$ 3-Amidino-9-methylphenanthridine, hydrochloride, 86.
 7-Amino-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 $C_{11}H_{14}O$ *cis*-1:2-Dihydroxy-3:4:5:6-dibenzcyclohepta-3:5-diene, 749.
 $C_{11}H_{14}O$ Javanicin, 1027.
 $C_{11}H_{14}O$ Oxyjavanicin, 1027.
 Substance, from green-tea infusions, and its acetyl derivative, 34.
 $C_{11}H_{14}N$ 7-Amino-2-anilino-4-methyl-1:8-naphthyridine, 1409.
 $C_{11}H_{14}N$ 2:8-Diamino-1:9-dimethylacridine, 247.
 2:8-Diamino-4:6-dimethylacridine, 248.
 2:7-Diamino-9:10-dimethylphenanthridine, salts, 72.
 $C_{11}H_{14}As$ 2-*p*-Tolylisoarsindoline, and its salts, 666.
 $C_{11}H_{14}O$ γ -6-Methoxy-1:2:3:4-tetrahydro-1-naphthylidenecrotonic acid, 1364.
 $C_{11}H_{14}N$ *N*-Benzyl-*N'*-methylbenzamidine, and its salts, 389.
 2-(1-Naphthylmethyl)-3:4:5:6-tetrahydropyrimidine, and its salts, 500.
 $C_{11}H_{14}O$ ψ -Santonin, constitution of, 1157.
 $C_{11}H_{14}O$ *d-cis*-3-Methylcyclohexyl hydrogen phthalate, 206.
 $C_{11}H_{14}N$ *pp'*-Bisaminomethyldiphenylmethane, 1454.
 $C_{11}H_{14}N$ Ethyl-*n*-butylbenzylacetonitrile, 741.
 $C_{11}H_{14}P$ *p*-isoPropylphenyldiallylphosphine, 1448.
 $C_{11}H_{14}P$ *p*-Tolyl-di- β -methylallylphosphine, 1449.
 $C_{11}H_{14}O$ 2-Homovanillylcyclohexanol, 1696.
 3-(2-Phenoxyethyl)hexane-1-carboxylic acid, and its *S*-benzylthiuronium salt, 224.
 $C_{11}H_{14}N$ 2-Amino-4- β -diethylaminoethylaminoquinoline, and its hydrate, 909.
 $C_{11}H_{14}N$ 2-Amino-4-anilino-6- β -diethylaminoethylamino-1:3:5-triazine, 159.
 $C_{11}H_{14}N$ α -Benzyl- α -ethyl- α -*n*-butylacetamidine, 741.
 $C_{11}H_{14}N$ 9- γ -Diethylaminopropyl-2:6:8-trimethylpurine, and its dipicrate, 51.
 $C_{11}H_{14}N$ *N*- δ -Diethylamino- α -methyl-*n*-butylphenylenediamines, 916.
 $C_{11}H_{16}S$ isoAmyl dihydromyrcene sulphide, 40.
 $C_{11}H_{16}N$ cycloHexyl-*n*-nonylamine, hydrochloride, 201.
 $C_{11}H_{16}Sn$ Tri-*n*-butylallyltin, 1450.
 $C_{11}H_{16}N$ 8-Aminopentadecane, and its *m*-nitrobenzenesulphonate, 198.
 Butylundecylamine, *m*-nitrobenzenesulphonate, 199.
 Methyl-*n*-hexyl-*n*-octylamine, oxalate, 200.

15 III

- $C_{11}H_8O_2N_2$ 7:8-Dinitroquinoline, 611.
 $C_{11}H_8O_2N_2$ 7-Nitroquinoline, 610.
 11-Nitroquinoline, 611.
 $C_{11}H_{10}O_2I_2$ 6:8-Di-iodo-3-phenyl-3:4-dihydrocoumarin, 204.
 $C_{11}H_{10}O_2N_2$ 2-(2':4'-Dinitrophenylamino)-3-methyleneisoindolinone, 837.
 2':4'-Dinitro-3-phenyl-1-methylphthalaz-4-one, 836.
 $C_{11}H_{10}N_2Cl_2$ 2-Chloro-4-*p*-chloroanilinoquinoline, 905.
 $C_{11}H_{10}N_2Cl_2$ 2-Chloro-4:6-di-*p*-chloroanilino-1:3:5-triazine, 159.
 $C_{11}H_{11}ON_2$ 5-Amino-2-cyano-7-methoxyacridine, 639.
 5-Amino-3-cyano-7-methoxyacridine, 640.
 $C_{11}H_{11}O_2I_2$ α -Phenyl- β -3:4:5-tri-iodophenylpropionic acid, 204.
 $C_{11}H_{11}O_2N_2$ Nitrophenyl-3-methylcinnoline *N*-oxides, 1651.
 $C_{11}H_{11}O_2N_2$ 4'-Nitro-2'-methoxy-3-phenylphthalaz-1-one, and its picrate, 464.
 4'-Nitro-2'-methoxy-3-phenylphthalaz-4-one, 465.
 $C_{11}H_{11}O_2N_2$ 1:4-Diketo-3-(4'-nitro-2'-methoxyphenyl)tetrahydrophthalazine, 464.
 $C_{11}H_{11}O_2Br$ Bromoanhydrojavanicin, 1028.
 $C_{11}H_{11}O_2Cl$ 7:8-Dihydroxyflavylium perchlorate, 349.
 $C_{11}H_{11}NCl_2$ 3:9-Dichloro-2:4-dimethyl-1-azanthracene, 547.
 $C_{11}H_{11}NS$ 1(or 3)-Methylthionaphthindole, and its picrate, 657.
 12-Methylthionaphthindole, and its picrate, 657.
 $C_{11}H_{11}NCl$ 7-Chloro-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 $C_{11}H_{11}ON$ 2-Acetamido-5-cyanodiphenyl, 85.
 4-*p*-Hydroxyphenyl-3-methylcinnoline, 1651.
 7-Hydroxy-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 4-Phenyl-3-methylcinnoline *N*-oxide, 1651.
 $C_{11}H_{11}O_2N$ α -Bis-(5-cyano-2-pyridyloxy)propane, 88.
 $C_{11}H_{11}O_2Br$ 3:5:3':5'-Tetrabromo- α -diphenoxypropane, 83.
 $C_{11}H_{11}O_2I_2$ α -Phenyl- β -3:5-di-iodophenylpropionic acid, 204.
 $C_{11}H_{11}O_2N$ 4-Cyano-4'-methoxydiphenylamine-2-carboxylic acid, 640.
 4-Nitro-4'-aminochalkone, 1419.

- $C_7H_5O_2N_4$ *o*-Carboxyacetophenone 2':4'-dinitrophenylhydrazone, 836.
 1:4-Dihydroxy-3-(2':4'-dinitrophenyl)-4-methyl-3:4-dihydrophthalazine, 836.
 $C_7H_5ON_3$ 4'-Nitro-3-phenyl-4-methylphthalaz-1-one nitrate, 836.
 $C_{12}H_9NCl$ Chloro-2:4-dimethyl-1-azanthracenes, 547, 548, 549.
 $C_{12}H_9ON$ 3-Chloro-2:4-dimethyl-5:6-benzoquinoline, 547.
 $C_{12}H_9N_2Cl$ 2-Amino-4:6-di-*p*-chloroanilino-1:3:5-triazine, hydrochloride, 159.
 $C_{12}H_9ON$ 5'-Hydroxy-2:4-dimethyl-5:6-benzoquinoline, 548.
 $C_{12}H_9ON$ 3-*p*-Hydroxyphenyl-2-methylindole, 1652.
 $C_{12}H_9ON$ 7-Amino-2-phenoxy-4-methyl-1:8-naphthyridine, 1409.
 $C_{12}H_9ON$ 4-Anilino-6-methoxycinnoline, 920.
 $C_{12}H_9ON$ 2-Carbethoxy-4:5-benzindole, 543.
 $C_{12}H_9ON$ 3:4'-Hydroxy-3'-methoxyphenylindole, 1695.
 $C_{12}H_9ON$ 3-Methylpiperolidine-2-picoline, and its methiodide, 1699.
 $C_{12}H_9ON$ 4'-Amino-2'-methoxy-3-phenylphthalaz-1-one, 466.
 $C_{12}H_9ON$ 4'-Amino-2'-methoxy-3-phenylphthalaz-4-one, 466.
 $C_{12}H_9ON$ 2-*p*-Anisidino-4-hydroxyquinazoline, 780.
 $C_{12}H_9ON_2$ *o*-Carboxybenzaldehyde *p*-nitro-*o*-methoxyphenylhydrazone, lactone form, 465.
 $C_{12}H_9ON_2$ 3'-Nitro-3-acetamidodiphenylamine-2-carboxylic acid, 597.
 $C_{12}H_9ON_2$ 6-Nitro-3'-acetamidodiphenylamine-2-carboxylic acid, 596.
 $C_{12}H_9N_2Cl$ 7-Amino-2-*p*-chloroanilino-4-methyl-1:8-naphthyridine, and its hydrochloride, 1409.
 $C_{12}H_9ON$ 4-Chloro-2-(6'-quinaldylamino)-6-methylpyrimidine, 1616.
 $C_{12}H_9ON$ 4:4'-Diaminochalkone, 1419.
 $C_{12}H_9ON$ 5-Amino-2-amidino-7-methoxyacridine, and its hydrochloride, 639.
 $C_{12}H_9ON$ 5-Amino-3-amidino-7-methoxyacridine, 641.
 $C_{12}H_9ON$ 2-(6'-Quinaldylamino)-4-hydroxy-6-methylpyrimidine, 1616.
 $C_{12}H_9ON$ 4'-Amino-2'-methoxy-*N*-phenylphthalimidine, 466.
 $C_{12}H_9ON$ 5-Amino-2-amidoximino-7-methoxyacridine, 639.
 $C_{12}H_9ON$ 2-(Methoxyquinolylamino)-4-hydroxy-6-methylpyrimidines, 1617.
 $C_{12}H_9ON$ 2-Nitro-4'-carbethoxyaminodiphenyl, 72.
 $C_{12}H_9ON$ 4:4'-Dinitro-*α*-diphenoxypropane, 391.
 $C_{12}H_9NAs$ Diphenyl-2-cyanoethylarsine, 621.
 $C_{12}H_9ON$ 4'-Methoxy-2-methyl-2-stilbazole, and its methiodide, 1698.
 $C_{12}H_9OAs$ 2-*p*-Anisylisoarsindoline, and its salts, 667.
 $C_{12}H_9ON$ 4-(7'-Hydroxy-2'-naphthylimino)pentan-2-one, 548.
 $C_{12}H_9ON$ 2:8-Diamino-3:7-dimethoxyacridine, 248.
 $C_{12}H_9OAs$ 2-*p*-Anisylisoarsindoline oxide, 667.
 $C_{12}H_9ON$ Diphenyl-2-carboxyethylarsine, 623.
 $C_{12}H_9N_2Cl$ 7-Amino-9:10-dimethylphenanthridinium chloride, 71.
 $C_{12}H_9N_2Br$ 7-Amino-9:10-dimethylphenanthridinium bromide, 71.
 $C_{12}H_9N_2I$ 7-Amino-9:10-dimethylphenanthridinium iodide, 71.
 $C_{12}H_9ON$ 5-Acetamidotetrahydroacridine, 636.
 $C_{12}H_9ON$ *N*-Benzylanisamidine, and its hydrochloride, 1115.
 $C_{12}H_9ON$ 6-Acetamidotetrahydroacridone, 637.
 $C_{12}H_9ON$ 2-Amino-4'-carbethoxyaminodiphenyl, 72.
 $C_{12}H_9ON$ 3-Nitro-4'-methoxy-4:5-dimethyldiphenylamine, 914.
 $C_{12}H_9ON$ 4-Nitro-4'-amino-*α*-diphenoxypropane, 394.
 $C_{12}H_9ON$ 2-Ketocyclohexylmalonic acid 2:4-dinitrophenylhydrazone, 1164.
 $C_{12}H_9ON$ 7-Acetyl-6-methyltetrahydrocarbazole, 939.
 $C_{12}H_9ON$ 1-Naphthyl β-dimethylaminoethyl ketone, hydrochloride, 1192.
 $C_{12}H_9ON$ Methoxy-1-methyl-1:2:3:4-tetrahydroacridones, 1038.
 $C_{12}H_9ON$ Methoxy-3-methyl-1:2:3:4-tetrahydroacridones, 1037.
 $C_{12}H_9OAs$ Phenyl-2-benzylloxyethylarsonic acid, and its salts, 624.
 $C_{12}H_9NCl$ 2-(1'-Naphthylmethyl)-3:4:5:6-tetrahydropyrimidinium chloride, 502.
 $C_{12}H_9NAs$ Diphenyl-2-amidinoethylarsine, and its salts, 622.
 $C_{12}H_9ON$ 3-Amino-4'-methoxy-4:5-dimethyldiphenylamine, and its picrate, 914.
 $C_{12}H_9ON$ 4:4'-Diamino-*α*-diphenoxypropane, 394.
 $C_{12}H_9ON$ Oct-2-en-4-ol 3:5-dinitrobenzoate, 758.
 $C_{12}H_9OP$ Triallylphosphine-*p*-benzoquinone, 1448.
 $C_{12}H_9ON$ Ethyl 2-*p*-anisidinocyclopent-1-enecarboxylate, 1037.
 $C_{12}H_9OCl$ Ethyl α-chloro-β-(2-methoxy-3:5-dimethylbenzoyl)propionate, 538.
 $C_{12}H_9OBr$ 3-Bromo 4:6-benzylidene 2-methyl α-methylglucoside, 17.
 $C_{12}H_9NCl$ 2-Chloro-4-β-diethylaminoethylaminoquinoline, and its hydrate, 904.
 $C_{12}H_9NCl$ 2-Chloro-4-*p*-chloroanilino-6-β-diethylaminoethylamino-1:3:5-triazine, and its hydrochloride, 159.
 $C_{12}H_9ON$ *N*-Benzoyl-4-propylpiperidine, 223.
 $C_{12}H_9ON$ 4-β-Diethylaminoethylamino-2-hydroxyquinoline, 904.
 $C_{12}H_9OP$ *p*-Methoxyphenyldi-β-methylallylphosphine, 1449.
 $C_{12}H_9ON$ 2-Methyl acetone L-arabinose anilide, 1344.
 $C_{12}H_9OBr$ Dihydro-ψ-santonin bromo-lactone, 1166.
 $C_{12}H_9NCl$ 2-Amino-4-*p*-chloroanilino-6-dimethylaminopropylaminopyrimidine, 1363.
 $C_{12}H_9ON$ 2-Chloro-4-anilino-6-β-diethylaminoethylamino-1:3:5-triazine, and its hydrochloride, 159.
 $C_{12}H_9ON$ Benzoyl derivative of α-ethyl-α-*n*-butylacetamide, 741.
 $C_{12}H_9NCl$ 2-Amino-4-*p*-chloroanilino-6-β-diethylaminoethylamino-1:3:5-triazine, 159.
 $C_{12}H_9IP$ Phenylmethyl-di-β-methylallylphosphonium iodide, 1449.
 $C_{12}H_9IAs$ Phenylmethyl-di-β-methylallylarsonium iodide, 1450.
 $C_{12}H_9ON$ *OO'*-Dibutyl benzhydroximate, 968.
 $C_{12}H_9ON$ Ethyl cyclohexenylbutylcyanoacetate, 773.
 $C_{12}H_9ON$ Ethyl β-(3:4-diethylcarbonatophenyl)serine, picrate, 660.
 $C_{12}H_9ON$ 4-Phenylureido-3:3-dimethylhexane, 1497.
 $C_{12}H_9ON$ 1-Diethylamino-1'-acetoxy-3-cyclohexylprop-2-yne, and its picrate, 1579.

- $C_{11}H_{17}ON$ 5-Acetamido-4- γ -diethylaminopropylamino-2:6-dimethylpyrimidine, and its flavianate, 50.
 $C_{11}H_{17}O_2N$ Ethyl 2- β -diethylaminoethylcyclohexanone-2-carboxylate, 400.
 $C_{11}H_{17}N_2Cl$ 4-Chloro-6- β -diethylamino- α -methylbutylamino-2:5-dimethylpyrimidine, 1358.
 $C_{11}H_{17}ON$ 4- β -Diethylamino- α -methylbutylamino-6-hydroxy-2:5-dimethylpyrimidine, dipicrate, 1358.
 $C_{11}H_{17}N_2S$ 4- β -Diethylamino- α -methylbutylamino-2-methylthio-6-methylpyrimidine, 787.
 $C_{11}H_{17}O_2N$ NN' -Dimethyltrimethylenediamine- NN' -biscarboxydiethylamide, 315.

15 IV

- $C_{11}H_9O_2NCl$ 4-Chloro-2-phthalimidobenzoic acid, 234.
 $C_{11}H_9ONS$ 6-Formylthionaphthindole, and its picrate, 657.
 $C_{11}H_9ONCl$ 5-Chloro-3-cyano-7-methoxyacridine, 640.
 $C_{11}H_9ONS$ 3-Hydroxy-2- m -nitrobenzoylthionaphthen, 1577.
 $C_{11}H_9O_2NCl$ Chloro-2:4-dimethyl-1-azanthraquinones, 548.
 $C_{11}H_{11}ONS$ 2-Phenacylbenzthiazole, 1621.
 $C_{11}H_{11}ONCl$ 4- p -Chloroanilino-2-hydroxyquinoline, 904.
 $C_{11}H_{11}ONF$ Fluoro-5-acetamidoacridines, 762.
 $C_{11}H_{11}O_2NS$ 3-Acetoxy-2-2'-pyridylthionaphthen, 1577.
 3-Keto-2-benzoyl-2:3-dihydrobenzthiazine, 1621.
 $C_{11}H_{11}O_2NS_2$ p -Nitrophenyl 2-amino-4-phenyl-5-thiazyl sulphide, 117.
 $C_{11}H_{11}ONS$ 2-Keto-1-phenylacetyl-1:2-dihydrobenzisothiazole S -oxide, 764.
 $C_{11}H_{11}O_2NS_2$ p -Nitrophenyl 2-amino-4-phenyl-5-thiazyl sulphone, 118.
 $C_{11}H_{11}NCIBr$ 9-Chloro-6-bromo-2:4-dimethyl-1-azanthracene, 548.
 $C_{11}H_{11}O_2NS$ 6-Methylthioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{11}H_{11}O_2NS_2$ 1:3-Bis- p -nitrobenzenesulphonylacetone, 117.
 $C_{11}H_{11}N_2ClS$ 2- p -Chloroanilino-4-methylthioquinazoline, 780.
 $C_{11}H_{11}ONCl$ 3-Chloro-4-(1'-chloro-2'-naphthylimino)pentan-2-one, 547.
 $C_{11}H_{11}ONS$ 2-Benzylidihydro-1:3-benzthiazine-4-one, 764.
 2-Dimethylaminothioxanthone, 1232.
 2-Ethylaminothioxanthone, 1233.
 $C_{11}H_{11}ONCl$ 4-Chloro-2-(methoxyquinolylamino)-6-methylpyrimidines, 1617.
 $C_{11}H_{11}ON_2$ α -Phenyl- β -(3:5-di-iodo-4-aminophenyl)propionic acid, 204.
 $C_{11}H_{11}ONS$ 2-Dimethylaminothioxanthone-3-sulphonic acid, and its potassium salt, 1233.
 $C_{11}H_{11}ONCl$ 3-Chloro-4-(2'-naphthylimino)pentan-2-one, 547.
 4-(1'-Chloro-2'-naphthylimino)pentan-2-one, 547.
 4-(Chloro-2'-naphthylimino)pentan-2-ones, 548, 549.
 $C_{11}H_{11}O_2NS$ 4-Methyl-2-(3'-phthalimidopropyl)thiazole, 1377.
 $C_{11}H_{11}O_2NS_2$ Triacetylaminio-2-mercapto-4-phenylthiazole, 1604.
 $C_{11}H_{11}O_2NS$ Ethyl 4:6-dihydroxy-3- p -nitrophenylthio-2-methylpyridine-5-carboxylate, 54.
 $C_{11}H_{11}O_2NS$ Ethyl 4:6-dihydroxy-3- p -nitrophenylsulphonyl-2-methylpyridine-5-carboxylate, 54.
 $C_{11}H_{11}ONCl$ 5-Chloro-7-acetamido-1:2:3:4-tetrahydroacridine, 636.
 5-Chloro-8-acetamido-1:2:3:4-tetrahydroacridine, 637.
 5-Chloro-9-acetamido-1:2:3:4-tetrahydroacridine, 637.
 $C_{11}H_{11}O_2NS$ 4-Dimethylamino-2'-carboxydiphenyl sulphide, 1231.
 4-Ethylamino-2'-carboxydiphenyl sulphide, 1232.
 $C_{11}H_{11}O_2NCl$ Ethyl pyruvate 1-chloro-2-naphthylhydrazones, 543.
 $C_{11}H_{11}ONS$ 4-Dimethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid, 1233.
 $C_{11}H_{11}O_2NS$ Ethyl 2-benzamidomethyl-4-thiazolylacetate, 1374.
 Ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate, 1373.
 $C_{11}H_{11}O_2NS_2$ 1:3-Disulphanilylacetone, 117.
 $C_{11}H_{11}ONS$ 3-(2'-Benzenesulphonylcarbamyphenyl-1'-thio)pentane-2:4-dione, 1576.
 $C_{11}H_{11}O_2NP$ Uridine-2'-phenyl phosphate, brucine salt, 340.
 $C_{11}H_{11}O_2NS$ 4:6-Dimethyl-2-acetylsulphanilamidopyrimidine, 1375.
 $C_{11}H_{11}O_2NS$ Sulphanilhomovanillylamide, and its hydrochloride, 616.
 $C_{11}H_{11}O_2NS_2$ p -Methylsulphonylbenzamidinum toluene- p -sulphonate, 1114.
 $C_{11}H_{11}O_2NS$ 4-Methyl-2-(3'-acetylsulphanilamidopropyl)thiazole, 1377.
 $C_{11}H_{11}ONCl$ 2-Chloro-4- β -diethylaminoethylamino-7-methoxyquinazoline, 899.
 $C_{11}H_{11}ONCl$ 2- p -Chloroanilino-4- β -diethylaminoethylamino-6-hydroxy-1:3:5-triazine, dihydrochloride, 159.
 $C_{11}H_{11}BrIP$ p -Bromophenylmethyl-di- β -methylallylphosphonium iodide, 1449.
 $C_{11}H_{11}O_2NS$ n -Butyl 3-ketoamyl sulphone 2:4-dinitrophenylhydrazones, 1516.
 $C_{11}H_{11}N_2IS$ Bis-2-(3-ethyl- Δ^2 -thiazoline)pentamethincyanine iodide, 1443.
 $C_{11}H_{11}O_2NS$ 3-Phenylureidodibutyl sulphone, 1516.
 $C_{11}H_{11}O_2NI$ Triethyl-2-hydroxyethylammonium iodide N -phenylurethane, 181.
 $C_{11}H_{11}O_2NS$ β - p -Acetamidobenzenesulphonyl- α -2-diethylaminoethylguanidine, 822.
 $C_{11}H_{11}ONBr$ 9-Keto-5-carbethoxy-2-ethylmorphane ethobromide, 400.
 $C_{11}H_{11}O_2NS$ 3-Nitro-1:5-di-(n -butylsulphonyl)-3-ethylpentane, 1516.

15 V

- $C_{11}H_{11}O_2N_2ClS$ Chloromethylthioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{11}H_{11}ONClBr$ 4-(1'-Chloro-6'-bromo-2'-naphthylimino)pentan-2-one, 548.

 C_{16} Group.

- $C_{16}H_{10}$ Pyrene, crystal structure of, 358.
 $C_{16}H_{20}$ Coprene, constitution of, 1338.

16 II

- $C_{16}H_8N_2$ 11-Cyanoquindoline, 610.
 $C_{16}H_8O_2$ 2':5-Dihydroxy-1-phenylnaphthalene, 226.
 $C_{16}H_{12}O_2$ *iso*Kämpferide, 124.
 Rhamnocitrin, constitution of, 122.

- $C_{15}H_{14}O_2$ Phenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone, 1096.
 $C_{15}H_{14}O_2$ 7-Methoxyflavylium hydroxide, salts, 349.
 $C_{15}H_{14}O_2$ β -Hydroxy- $\alpha\beta$ -diphenylbutyric acid, 1698.
 $C_{15}H_{14}O_2$ 2:2'-Dimethoxybenzilic acid, 953.
 $C_{15}H_{15}N_2$ 2-Amino-8-methylamino-3:7-dimethylacridine, 249.
 $C_{15}H_{15}O_2$ 1-Keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene-2- α -propionic lactone, 539.
Methyl γ -6-methoxy-1:2:3:4-tetrahydro-1-naphthylideneacetonate, 1365.
 $C_{15}H_{15}N_2$ *pp'*-Bisaminomethylstilbene, 1454.
4'-Dimethylamino-3-methyl-2-stilbazole, and its methiodide, 1699.
 $C_{15}H_{20}O_4$ Ethyl 1-keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene-2-carboxylate, 538.
 $C_{15}H_{20}O_4$ α -(2-Methoxy-3:5-dimethylbenzoyl)butane- $\beta\gamma$ -dicarboxylic acid, 538.
 $C_{15}H_{20}O_4$ α -(β -2-Methoxy-3:5-dimethylphenylethyl)- α' -methylsuccinic acid, 538.
 $C_{15}H_{22}N_2$ 4- γ -Diethylaminopropylaminoquinoline, 904.
 $C_{15}H_{22}P$ *p*-Ethylphenyl-di- β -methylallylphosphine, 1449.
p-Xylyl-di- β -methylallylphosphine, 1449.
 $C_{15}H_{24}N_2$ 2-Amino-4- γ -diethylaminopropylaminoquinoline, 909.
 $C_{15}H_{24}S$ Phenyl dihydromyrcene sulphide, 40.
 $C_{15}H_{25}N$ Ethyl-*n*-butyl-*n*-octylacetoneitrile, 741.
Ethyl-*n*-butyl-*sec*-octylacetoneitrile, 741.
 $C_{15}H_{25}N$ *cyclo*Hexyl-*n*-nonylamine, hydrobromide, 201.
 $C_{15}H_{25}N_2$ 2-Amino-4:6-bis-(β -diethylaminoethylamino)pyrimidine, 47.
 $C_{15}H_{25}N_2$ α -Ethyl- α -*n*-butylacet-*N*-*n*-octylamidine, 741.
 α -Ethyl- α -*n*-butylacet-*N*-*sec*-octylamidine, salts, 741.
 α -Ethyl- α -*n*-butyl- α -*n*-octylacetamidine, 741.
 α -Ethyl- α -*n*-butyl- α -*sec*-octylacetamidine, hydrochloride, 741.
 $C_{15}H_{25}N$ 2-Amino-3-methylpentadecane, 1499.
Di-*n*-octylamine, *m*-nitrobenzenesulphonate, 199.
2-Octylamino-octane, salts, 199.

16 III

- $C_{16}H_{18}SAs_2$ Bis-2-isoarsindolyl sulphide, 667.
 $C_{16}H_{18}N_2Cl_2$ 2:5-Dichloro-3:4:2':3'-pyridoacridine, 680.
 $C_{16}H_{18}O_2N_2$ 7-Nitroquinoline-11-carboxylic acid, and its nitrate, 611.
 $C_{16}H_{18}O_2N_2$ 6-Nitro-1:2-naphtho-*p*-nitrophenyltriazole, 1061.
 $C_{16}H_{18}O_2N_2$ 6- and 7-Nitro-1-*p*-nitrobenzeneazo-2-naphthols, 1061.
 $C_{16}H_{18}O_2N_2$ 2:5-Diketo-3-(2':4'-dinitrophenyl)isoindolinopyrazolidocoline, 832.
 $C_{16}H_{17}ON$ 2-Methylphenanthroxazole, 652.
 $C_{16}H_{17}ON_2$ Quindoline-11-carboxamide, 610.
 $C_{16}H_{17}O_2N_2$ 7-Aminoquinoline-11-carboxylic acid, 611.
 $C_{16}H_{17}O_2N_2$ 2:5-Diketo-3-(4'-nitrophenyl)isoindolinopyrazolidocoline, 470.
 $C_{16}H_{17}O_2N_2$ 6-Nitro-*p*-nitrobenzeneazo-2-naphthylamine, 1061.
7-Nitro-1-*p*-nitrobenzeneazo-2-naphthylamine, 1061.
 $C_{16}H_{17}O_2N_2$ 4-*p*-Acetoxyphenylcinoline, 1651.
 $C_{16}H_{17}O_2N_2$ 2:5-Diketo-3-(2'-nitro-4'-aminophenyl)isoindolinopyrazolidocoline, 832.
 $C_{16}H_{17}O_2N_2$ 2-(2':4'-Dinitrophenylamino)isoindolinone-3-acetic acid, 832.
1-Hydroxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine-4-acetic acid, 833.
 $C_{16}H_{17}NBr$ *cis*-4-Bromo-4'-cyano-2-methylstilbene, 691.
 $C_{16}H_{17}NCl_2$ 4-Chloro-2-*p*-chloroanilino-3-methylquinoline, 908.
 $C_{16}H_{17}N_2S_2$ Schiff's base, from 5-amino-2-mercapto-4-phenylthiazole, 1603.
 $C_{16}H_{17}N_2Cl_2$ 4-Chloro-2-amino-6-*p*-chloroanilino-5-phenylpyrimidine, 1362.
 $C_{16}H_{17}O_2N_2$ 2:5-Diketo-3-(4'-aminophenyl)isoindolinopyrazolidocoline, 471.
 $C_{16}H_{17}O_2Cl$ 1-*p*-Chlorophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone, 1095.
 $C_{16}H_{17}O_2Br$ 1-*p*-Bromophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone, 1095.
 $C_{16}H_{17}O_2F$ 1-*p*-Fluorophenyl-1:4:9:10-tetrahydronaphtha-5:8-quinone, 1095.
 $C_{16}H_{17}O_2Br$ 5-Bromo-2-benzoyloxy-4-methylacetophenone, 230.
 $C_{16}H_{17}O_2N_2$ 4'-Nitro-2'-methoxy-3-phenyl-1-methylphthalaz-4-one, 467.
4'-Nitro-2'-methoxy-3-phenyl-4-methylphthalaz-1-one, and its picrate, 466.
 $C_{16}H_{17}O_2N_2$ 2-(4'-Nitrophenylamino)isoindolinone-3-acetic acid, 470.
 $C_{16}H_{17}NS$ 2:10-Dimethylthionaphthindole, 657.
 $C_{16}H_{17}NS_2$ 2-Benzylthio-4-phenylthiazole, 1658.
 $C_{16}H_{17}O_2N_2$ 4-*p*-Anisyl-3-methylcinoline *N*-oxide, 1651.
3-Nitro-1:2-diphenyl-*n*-propyl cyanide, 1508.
 $C_{16}H_{17}O_2N_2$ 1-Hydroxy-3-(2':4'-diaminophenyl)-3:4-dihydrophthalazine-4-acetic acid lactam, 834.
 $C_{16}H_{17}O_2Br_2$ 2:2'-Dibromo-5:5'-dimethoxystilbene, and its dibromide, 1452.
 $C_{16}H_{17}O_2Br_2$ 5:5'-Dibromo-2:2'-dimethoxybenzilic acid, 953.
 $C_{16}H_{17}O_2N_2$ 1:4-Dimethoxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine, 835.
1-Hydroxy-4-methoxy-3-(2':4'-dinitrophenyl)-4-methyl-3:4-dihydrophthalazine, 836.
 $C_{16}H_{17}N_2Br$ 5-Bromo-*o*-tolualdazine, 692.
 $C_{16}H_{17}N_2S_2$ 5-Amino-2-benzylthio-4-phenylthiazole, 1604.
2:4-Dithio-5-phenyl-1(or 3)-benzylhydantoin, 1607.
 $C_{16}H_{17}ON$ 3-*p*-Anisyl-2-methylindole, and its picrate, 1652.
 $C_{16}H_{17}ON_2$ 4- α -Pyridylamino-6-methoxyquinaldine, 1553.
 $C_{16}H_{17}O_2N_2$ 4'-Amino-2'-methoxy-3-phenyl-1-methylphthalaz-4-one, 467.
4'-Amino-2'-methoxy-3-phenyl-4-methylphthalaz-1-one, 467.
 $C_{16}H_{17}O_2Br$ 5-Bromo-2:2'-dimethoxystilbene, and its dibromide, 1451.
 $C_{16}H_{17}O_2N$ *O*-Acetylvaniilmanil, 616.
1-*N*- α -Phenylethylphthalamic acid, and its silver salt, 510.
 $C_{16}H_{17}O_2N_2$ *o*-Carboxyacetophenone *p*-nitro-*o*-methoxyphenylhydrazone, 467.

- $C_{12}H_{11}O_2N_2$ 4'-Amino-2'-methoxy-*N*-phenyl-3-methylphthalimidine, 468.
 12-Diacetamido-2,3-dihydro- β -quinidine, 635.
 3-Nitro-1-(1-naphthyl)-2,2-dimethylpropyl cyanide, 1505.
 $C_{11}H_{10}O_2N_2$ *O*-Acetylvanill- N^1 -phenylamidine, 616.
 $C_{11}H_{10}O_2N_2$ Bis-(*p*-nitrobenzylmethyleneimine, 1117.
 $C_{11}H_{10}O_2N_2$ 3':5'-Benzylidene uridine, 340.
 $C_{11}H_{10}O_2N_2$ 2-Picrylamino-3-phenylbutane, 1499.
 $C_{11}H_{17}ON$ 3-(*p*-Xylidino-4:5-coumaran, hydrochloride, 1047.
 $C_{11}H_{17}O_2As$ Diphenyl-2-carboxy-*n*-propylarsine, 623.
 $C_{11}H_{17}ON$ Triacetyl-2:3-dimethylindole, 1633.
 $C_{11}H_{17}O_2N_2$ 4:8-Diacetamido-1:5-dimethoxynaphthalene, 354.
 3-Dimethylaminophenol *N*-benzylurethane, methiodide, 189.
 $C_{11}H_{12}O_2N_2$ Ethylenedi-*O*-benzamidoxime, dihydrochloride, 968.
 $C_{11}H_{12}O_2S$ Methylcyclohexyl phenyl sulphones, 40.
 $C_{11}H_{11}IAs$ 2-*p*-Tolyl-2-methylisoarsindolinium iodide, and its picrate, 666.
 $C_{11}H_{11}ON$ 1:3:3-Trimethyl-2-pent-(2'-en-4'-onylidene)dihydroindole, 1630.
 $C_{11}H_{11}O_2N$ Methoxy-3-ethyl-1:2:3:4-tetrahydroacridones, 1038.
 7-Methoxy-1-ethyl-1:2:3:4-tetrahydroacridone, 1038.
 $C_{11}H_{10}ON$ 4:4'-Bis(dimethylamino)azoxybenzene, and its salts, 559.
 $C_{11}H_{10}O_2N_2$ $\alpha\beta$:2:2'-Difurylthane-5:5'-di-iminoether, and its dihydrochloride, 398.
 $C_{11}H_{10}O_2N_2$ Difurfuryl ether 5:5'-di-iminoether, dihydrochloride, 397.
 $C_{11}H_{10}O_2N_2$ 2-Ketocyclohexyl- α -isobutyric acid 2:4-dinitrophenylhydrazone, 1166.
 $C_{11}H_{10}O_2N_2$ 1-Triacetyl-1-arabinosidoglyoxaline-4:5-dicarboxamide, 380.
 $C_{11}H_{11}O_2N$ Ethyl 2-*p*-phenetidinocyclopent-1-ene carboxylate, 1037.
 $C_{11}H_{12}N_2Cl_2$ 2:7-Dichloro-4- γ -diethylaminopropylaminoquinoline, dipicrate, 906.
 $C_{11}H_{12}ON_2$ 3-(2-Benzamidoethyl)hexyl cyanide, 223.
 $C_{11}H_{12}O_2S$ 2-*p*-Toluenesulphonyl 3:4-acetone β -methyl-*n*-arabinoside, 1343.
 2-*p*-Toluenesulphonyl 3:4-acetone β -methyl-*L*-arabinoside, 1343.
 5-*p*-Toluenesulphonyl 3-methyl 1:2-acetone *L*-arabofuranose, 1063.
 2-*p*-Tosyl 3:4-isopropylidene β -methyl-*L*-arabopyranoside, 971.
 $C_{11}H_{12}N_2Cl$ 2-Chloro-4- γ -diethylaminopropylaminoquinoline, and its dipicrate, 904.
 $C_{11}H_{12}ON_2$ 4- γ -Diethylaminopropylamino-2-hydroxyquinoline, 903.
 $C_{11}H_{12}ON_2$ 2-Amino-4- β -diethylaminoethylamino-5-phenoxy-pyrimidine, 46.
 $C_{11}H_{12}O_2N_2$ 2-Succinimido-3:6-di-*sec*-butylpyrazine, 377.
 $C_{11}H_{12}N_2Cl$ 2-Amino-4-*p*-chloroanilino-6- β -diethylaminoethylaminopyrimidine, 1362.
 2-*p*-Chloroanilino-6- β -diethylaminoethylamino-4-methyl-1:3:5-triazine, 158.
 $C_{11}H_{12}O_2N_2$ 2-Dimethylamino-3-cyclohexylphenol *N*-methylurethane, and its methiodide, 189.
 $C_{11}H_{12}IP$ *p*-Tolylmethyl-di- β -methylallylphosphonium iodide, 1449.
 $C_{11}H_{12}O_2N_2$ 2-Succinamido-3:6-di-*sec*-butylpyrazine, 377.
 $C_{11}H_{12}O_2N_2$ *NN'*-Dimethyltrimethylenediamine-*N*-carboxydiethylamide-*N'*-carboxypiperide, 315.
 $C_{11}H_{12}O_2N_2$ 1:10-Decamethylenedioxydiurethane, 967.
 $C_{11}H_{12}O_2TI$ Dipropylthallium tartrate, 1384.
 $C_{11}H_{12}ON$ Formamidopentadecane, 198.
 $C_{11}H_{12}ON$ 2-Nitro-3-methylpentadecane, 1499.
 $C_{11}H_{12}ON_2$ *NN'*-Pentamethylene-*N'*-2-ethoxyethyl-*N'*-(2-ethoxyethylaminoethyl)urea, 315.
 $C_{11}H_{12}ON_2$ Tri-diethylthallium tartrate, 1384.
 $C_{11}H_{12}O_2N_2$ *NN'*-Diethylethylenediamine-*NN'*-biscarboxydiethylamide, 315.
 $C_{11}H_{12}O_2P$ Diethyl *n*-dodecylphosphonate, 1466.

16 IV

- $C_{11}H_9O_2N_2Br$ 7-Bromoquinoline-11-carboxylic acid, 609.
 $C_{11}H_9O_2N_2Cl_2$ 2:5-Diketo-3-(2':6'-dichloro-4'-nitrophenyl)isoindolinopyrazolidocoline, 472.
 $C_{11}H_9O_2N_2Br_2$ 2:5-Diketo-3-(2':6'-dibromo-4'-nitrophenyl)isoindolinopyrazolidocoline, 473.
 $C_{11}H_9O_2N_2Cl_2$ 4:8'-Dichloro-6'-quinolylanthranilic acid, 680.
 $C_{11}H_9O_2N_2Cl$ 2:5-Diketo-3-(2'-chloro-4'-nitrophenyl)isoindolinopyrazolidocoline, 471.
 $C_{11}H_9O_2N_2Br$ 2:5-Diketo-3-(2'-bromo-4'-nitrophenyl)isoindolinopyrazolidocoline, 473.
 $C_{11}H_9O_2N_2Cl$ Quindoline-11-carboxylic acid, 609.
 $C_{11}H_{11}O_2N_2I$ α -Iodo-4-*p*-acetoxyphenylcinoline, 1655.
 $C_{11}H_{11}O_2N_2Cl$ 6- and 7-Nitro-1-*p*-chlorobenzeneazo-2-naphthylamines, 1061.
 $C_{11}H_{11}O_2N_2Cl_2$ 2-(2':6'-Dichloro-4'-nitrophenylamino)isoindolinone-3-acetic acid, 472.
 $C_{11}H_{11}O_2N_2Br_2$ 2-(2':6'-Dibromo-4'-nitrophenylamino)isoindolinone-3-acetic acid, 473.
 $C_{11}H_{11}ON_2I$ 1-Iodo-3-acetyl-2-phenylpyrrocoline, 672.
 $C_{11}H_{11}O_2N_2Cl$ 2:5-Diketo-3-(2'-chloro-4'-aminophenyl)isoindolinopyrazolidocoline, 471.
 $C_{11}H_{11}O_2N_2Cl$ 2-(2'-Chloro-4'-nitrophenylamino)isoindolinone-3-acetic acid, 471.
 $C_{11}H_{11}O_2N_2Br$ 2-(2'-Bromo-4'-nitrophenylamino)isoindolinone-3-acetic acid, 473.
 $C_{11}H_{11}O_2N_2S$ Benzaldehyde 2':4'-dinitrophenylhydrazone- ω -sulphonic-2- β -acrylic acid, 832.
 3-(2':4'-Dinitrophenyl)-3:4-dihydrophthalazine-1-sulphonic-4-acetic acid, sodium hydrogen salt, 833.
 $C_{11}H_{11}NCS$ 10-Chloro-2:12-dimethylthionaphthindole, and its picrate, 657.
 $C_{11}H_{11}ONS$ 11-Ethoxythionaphthindole, 657.
 $C_{11}H_{11}ON_2Cl_2$ 2-Chloro-4-*p*-chloroanilino-6-*p*-anisidino-1:3:5-triazine, 159.
 $C_{11}H_{11}OCl_2Fe$ 6-Methylflavylium ferrichloride, 349.
 $C_{11}H_{11}O_2NS$ *N*-Benzoyl derivative of 2-methyl-1,3-benzthiazine-4-one, 764.
 $C_{11}H_{11}O_2N_2S$ 6-Nitro-3-methyl-2-anilinoethylidenebenzthiazoline, 957.
 $C_{11}H_{11}O_2N_2S$ 5-Amino-4-*p*-nitrobenzeneazo-2-benzylthiazole, 1597.
 $C_{11}H_{11}O_2NS$ 2-Acetamido-2'-carboxy-5-methoxydiphenyl sulphide, 1233.
 $C_{11}H_{11}O_2NS$ 2-Acetamido-2'-carboxy-5-methoxydiphenyl sulphone, 1233.
 $C_{11}H_{11}O_2N_2S$ 3-Keto-2-acetyl-2:3-dihydrobenzthiazine 2:4-dinitrophenylhydrazone, 1621.
 $C_{11}H_{11}N_2Cl_2S_2$ Bis-2-(5-2-thienylpyrrole)azamethin dihydrochloride, 1200.
 $C_{11}H_{11}ONCl$ 2-(5-Chloro-2-benzamidophenyl)propylene, 810.

- $C_9H_7O_2N_2Cl$ 2-*p*-Chloroanilino-4-ethoxyquinazoline, 780.
 $C_9H_7O_2N_2Cl$ 2-(2'-Chloro-4'-aminophenylamino)isoindolinone-3-acetic acid, 472.
 $C_{10}H_7O_4N_2S$ 6-Ethoxythioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{10}H_7O_4N_2Cl$ 4'-Nitro-1:2'-dimethoxy-3-phenylphthalazinium perchlorate, 465.
 $C_{10}H_7O_4NS$ 2-Methylethylaminothioxanthone, 1233.
 $C_{10}H_7ON_2I$ 4-*p*-Hydroxyphenylcinnoline ethiodide, 1655.
 $C_{10}H_7ON_2Cl$ 2-Amino-4-*p*-chloroanilino-6-*p*-anisidino-1:3:5-triazine, hydrochloride, 160.
 $C_{10}H_7OCl_2As$ *As-spiro*-Bis-5-chloroisosarsindolinium hydroxide, salts, 669.
 $C_{10}H_7O_2NS$ 4-Methylacetamido-2'-carboxydiphenyl sulphide, 1232.
 $C_{10}H_7O_2N_2Cl$ 4'-Chloro-3-nitro-*N*-aceto-4:5-dimethyldiphenylamide, 913.
 $C_{10}H_7O_2NCl$ 2-Chloro-2-benzamidophenyldimethylcarbinol, 810.
 $C_{10}H_7O_2N_2$ 6-Chloro-7:9-diacetyltetrahydrocarbazole, 939.
 $C_{10}H_7O_2NBr$ 6-Bromo-7:9-diacetyltetrahydrocarbazole, 939.
 $C_{10}H_7O_2N_2S$ Di-(2-nitro-1-phenylethyl) sulphide, 1481.
 $C_{10}H_7O_2N_2S$ 6-Benzylthiopropaldehyde dinitrophenylhydrazones, 1611.
 $C_{10}H_7O_2N_2S_2$ 6-Nitro-2-methylbenzthiazole metho-*p*-toluenesulphonate, 957.
 $C_{10}H_7ON_2Cl$ 4'-Chloro-3-amino-*N*-aceto-4:5-dimethyldiphenylamide, and its salts, 913.
 $C_{10}H_7O_2NS$ 4-Methylethylamino-2'-carboxydiphenyl sulphide, 1232.
 $C_{10}H_7O_2NS$ *p*-Tolyl-2-benzamidoethyl sulphone, 1481.
 $C_{10}H_7O_2NS$ *N*-Benzoyltoluene-*p*-sulphonethylamide, 387.
 $C_{10}H_7O_2NS_2$ 4-Methylethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid, 1233.
 $C_{10}H_7O_2NS_2$ 5-Acetylsulphanilamido-2-benzylthiazole, 1597.
 $C_{10}H_7O_2NBr$ 6-Bromo-10:11-dihydroxy-7:9-diacetylhexahydrocarbazole, 939.
 $C_{10}H_7O_2NS_2$ [2-(4-Methyl-3-ethylthiazole)][2-(3-phenyl-4-methylthiazole)]azamethincyanine iodide, 1658.
 $C_{10}H_7O_2NS_2$ Ethyl 2-*N*⁴-acetylsulphanilamido-4-methylthiazole-5-acetate, and its hydrochloride, 591.
 $C_{10}H_7O_2NS$ Sulphanil- α -vanillylethylamide, and its hydrochloride, 616.
 $C_{10}H_7ON_2Cl$ 7-Chloro-4- γ -diethylaminopropylamino-2-hydroxyquinoline, 906.
 $C_{10}H_7O_2Cl_2As$ Dichlorobis(phenyldimethylarsine)palladium, 665.
 $C_{10}H_7ON_2Cl$ 2-Chloro-4-*p*-anisidino-6- β -diethylaminoethylamino-1:3:5-triazine, hydrochloride, 159.
 $C_{10}H_7O_2N_2P$ *p*-Methoxyphenylmethyl-di- β -methylallylphosphonium iodide, 1449.
 $C_{10}H_7O_2N_2Cl$ Trimethyl-2-hydroxyethylammonium chloride *N*-dipropylurethane, 180.
 $C_{10}H_7O_2NS_2$ 3-Acetamido-1:5-di-(*n*-butylsulphonyl)-3-methylpentane, 1516.
 $C_{10}H_7ON_2I_2$ 2:2'-Dipiperidinoisopropylurea dimethiodide, 1513.

C₁₇ Group.

- $C_{17}H_{15}N_2$ *cis*- and *trans*-4:4'-Dicyano-2-methylstilbene, 691.
 $C_{17}H_{15}O_2$ Methyl dibenznorcaradienecarboxylate, 750.
 $C_{17}H_{15}O_6$ Acetylanhydrojavanicin, 1027.
 $C_{17}H_{15}N_4$ *NN'*-Di-2-pyridylbenzamidine, 389.
 $C_{17}H_{15}O_2$ 6-Methoxy-2-*p*-methoxyphenylindene, 1697.
 $C_{17}H_{15}O_2$ 1-(*o*-Tolyl)-1:4:9:10-tetrahydronaphthaquinone, 1094.
 $C_{17}H_{15}O_2$ *p*-Tolyl-1:4:9:10-tetrahydronaphtha-5:8-quinone, 1094.
 $C_{17}H_{15}O_2$ 3-Acetoxy-2-methoxy-9:10-dihydrophenanthrene, 1696.
 $C_{17}H_{15}O_2$ 1-*p*-Anisyl-1:4:9:10-tetrahydronaphthaquinone, 1096.
 $C_{17}H_{15}O_2$ *O*-Carbobenzoyloxymovanillin, 1695.
 $C_{17}H_{15}N_4$ *trans*-4:4'-Diamidino-2-methylstilbene, dihydrochloride, 691.
 $C_{17}H_{15}N_3$ 2:8-Bismethylamino-3:7-dimethylacridine, 249.
 $C_{17}H_{15}O_4$ 2-*O*-Acetylhomovanillylidene α -cyclohexanone, 1696.
 $C_{17}H_{15}O_2P$ Ethyl 1-keto-5-methoxy-6:8-dimethyl-1:2:3:4-tetrahydronaphthalene-2-glyoxylate, 538.
 $C_{17}H_{15}P$ *p*-isoPropylphenyl-di- β -methylallylphosphine, 1449.
 $C_{17}H_{15}N_6$ 2-Amino-4-*p*-toluidino-6-diethylaminoethylaminopyrimidine, 1363.
 $C_{17}H_{15}N_2$ *NN'*-Di-*n*-amylbenzamidine, and its picrate, 388.
 $C_{17}H_{15}N_2$ 9- γ -Diethylamino- α -methyl-*n*-butyl-2:6:8-trimethylpurine, 51.
 $C_{17}H_{15}N_3$ 5-Amino-3-(8-diethylamino- α -methyl-*n*-butylamino)-*o*-xylene, 912.
 $C_{17}H_{15}N_3$ 1:11-Bis-(2'-dihydroglyoxalyl)undecane, and its toluene-*p*-sulphonate, 500.
 $C_{17}H_{15}N_5$ 4-Amino-2- γ -di-*n*-butylaminopropylamino-5:6-dimethylpyrimidine, and its dipicrate, 48.
 $C_{17}H_{15}N_5$ 5-Amino-4- γ -di-*n*-butylaminopropylamino-2:6-dimethylpyrimidine, 50.
 $C_{17}H_{15}N$ 1-Aminoheptadecane, and its salts, 199.
 $C_{17}H_{15}N$ *iso*Amyldi-*n*-hexylamine, oxalate, 200.

17 III

- $C_{17}H_{15}N_2Cl_2$ 5:8-Dichloro-2-methyl-3:4:2':3'-pyridoacridine, 681.
 $C_{17}H_{15}O_2N_2$ Acetyl-7-nitroquindoline, 610.
 $C_{17}H_{15}O_2N_3$ 6:4'- and 7:4'-Dinitrobenzylidene-2-naphthylamines, 330.
 $C_{17}H_{15}O_2N_3$ Substance from 4-methylcinnoline-7-carboxylic acid and *o*-nitrobenzaldehyde, 810.
 $C_{17}H_{15}O_2N_2$ Methyl quindoline-11-carboxylate, 610.
 $C_{17}H_{15}O_2N_4$ 5-Methoxy-1:4-naphthaquinone 2:4-dinitrophenylhydrazones, 354.
 $C_{17}H_{15}N_3S$ 6-(2-Cyanoethyl)thionaphthindole, 658.
 $C_{17}H_{15}O_2N_2$ 2:5-Diketo-3-(4'-nitro-2'-methylphenyl)isoindolinopyrazolidocoline, 473.
 $C_{17}H_{15}O_2N_2$ 2:5-Diketo-3-(4'-nitro-2'-methoxyphenyl)isoindolinopyrazolidocoline, 465.
 $C_{17}H_{15}O_2N_2$ Benzo-1'-(2':4'-dinitrophenyl)-1'-methylhydrazide-2- β -acrylonitrile, 833.
 $C_{17}H_{15}NS$ 4:6-Trimethylenethionaphthindole, and its picrate, 657.
 $C_{17}H_{15}N_2Cl_2$ 4-Chloro-6-*p*-chloroanilino-5-phenyl-2-methylpyrimidine, 1361.
 $C_{17}H_{15}O_2N_2$ 6-Nitro-1-*p*-tolylazo-2-naphthylamine, 1061.
 $C_{17}H_{15}O_2Br_2$ *cis*-4:4'-Dibromo-2:2'-dimethylstilbene- α -carboxylic acid, 692.
 $C_{17}H_{15}O_2N_4$ 1-Keto-3-(2':4'-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetic acid, 834.
 $C_{17}H_{15}O_2N_4$ Methyl 2-(2':4'-dinitrophenylamino)isoindolinone-3-acetate, 832.
 $C_{17}H_{15}O_2N_4$ Methyl 1-hydroxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine-4-acetate, 833.

- $C_{17}H_{11}N_2Cl$ 4-Chloro-2-*p*-chloroanilino-3-ethylquinoline, 909.
 $C_{17}H_{11}N_2S$ Schiff's base, from 5-amino-2-mercaptotiazole, 1603.
 $C_{17}H_{11}ON$ *p*-Amino- ω -cinnamylideneacetophenone, 1420.
 $C_{17}H_{11}ON$ 7-Acetamido-4-phenyl-2-methyl-1:8-naphthyridine, and its salts, 1410.
 $C_{17}H_{11}O_2N$ Hex-3-en-5-yn-2-yl α -naphthylurethane, 1585.
 $C_{17}H_{11}O_2N$ 7-Acetamido-2-phenoxy-4-methyl-1:8-naphthyridine, 1409.
 $C_{17}H_{11}O_2N$ 1:9-Diacetamidooacridine, 1419.
 $C_{17}H_{11}O_2N$ 3-*O*-4'-Acetoxy-3'-methoxyphenylindole, 1695.
 $C_{17}H_{11}O_2N$ *N*-Benzoyl-1:2:3:4-tetrahydroisoquinolinaldic acid, 129.
 $C_{17}H_{11}O_2N$ 4'-Acetamido-2'-methoxy-3-phenylphthalaz-1-one, 466.
 $C_{17}H_{11}O_2N$ 4'-Acetamido-2'-methoxy-3-phenylphthalaz-4-one, 466.
 $C_{17}H_{11}O_2N$ 4'-Nitro-1:2'-dimethoxy-3-phenyl-4-methylene-3:4-dihydrophthalazine, 467.
 $C_{17}H_{11}O_2N$ Methyl 2-(4'-nitrophenylamino)isoindolinone-3-acetate, 470.
 $C_{17}H_{11}O_2N$ 2-(4'-Nitro-2'-methylphenylamino)isoindolinone-3-acetic acid, 473.
 $C_{17}H_{11}O_2N$ 1-Hydroxy-3-(4'-nitro-2'-methoxyphenyl)-3:4-dihydrophthalazine-4-acetic acid, 464.
 $C_{17}H_{11}O_2N$ 2-(4'-Nitro-2'-methoxyphenylamino)isoindolinone-3-acetic acid, 464.
 $C_{17}H_{11}ON$ 3-Ethyl-2-aniloehtylidenebenzoxazoline, 959.
 $C_{17}H_{11}O_2N$ 7-Carbethoxyamino-9-methylphenanthridine, 71.
 $C_{17}H_{11}O_2N$ 3-Nitro-1:2-diphenyl-*n*-butyl cyanide, 1508.
 $C_{17}H_{11}O_2N$ $\alpha\alpha$ -Bis-(5-cyano-2-pyridyloxy)pentane, 88.
 $C_{17}H_{11}O_2N$ α -Cyano- α' -carbamyldibenzylurea, 1608.
 $C_{17}H_{11}O_2N$ 4'-Acetamido-2'-methoxy-*N*-phenylphthalimidine, 466.
 $C_{17}H_{11}O_2N$ 1-Methoxy-4-ethoxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine, 835.
 $C_{17}H_{11}O_2N$ *O*-Acetylhomovanillin 2:4-dinitrophenylhydrazone, 1694.
 $C_{17}H_{11}N_2Se$ 3-Ethyl-2-aniloehtylidenebenzelenazoline, 958.
 $C_{17}H_{11}ON$ 2-Amino-8-acetamido-1:9-dimethylacridine, 247.
 $C_{17}H_{11}O_2N$ 1-Hydroxy-3-(4'-amino-2'-methoxyphenyl)-3:4-dihydrophthalazine-4-acetic acid, 464.
 $C_{17}H_{11}N$ 4-Phenyl-3-methylcinnoline ethiodide, 1654.
 $C_{17}H_{11}O_2N$ 5-Diacetamidotetrahydroacridine, 636.
 $C_{17}H_{11}O_2N$ 2-Amino-4:6-di-*p*-anisidino-1:3:5-triazine, hydrochloride, 159.
 $C_{17}H_{11}O_2N$ 2-Acetamido-4'-carbethoxyaminodiphenyl, 70.
 $C_{17}H_{11}O_2N$ 3-Deoxy-*l*-xylose *p*-nitrophenylosazone, 972.
 $C_{17}H_{11}O_2N$ 7:9-Diacetyl-6-methyltetrahydrocarbazole, 939.
 $C_{17}H_{11}O_2N$ 5:7-Diacetamido-1:2:3:4-tetrahydroacridine, 636.
 $C_{17}H_{11}O_2N$ 2:8-Diamino-3:7-diethoxyacridine, 248.
 $C_{17}H_{11}O_2N$ 2-*o*-Methoxymethylphenylethyl *N*-phenylcarbamate, 1640.
 $C_{17}H_{11}O_2N$ β -Anilino- α -amidino- β -3-methoxy-4-hydroxyphenylpropionamide, hydrochloride, 618.
 $C_{17}H_{11}O_2N$ 3-Dimethylaminophenol *N*-4-methoxybenzylurethane, methiodide, 189.
 $C_{17}H_{11}O_2N$ $\alpha\alpha$ -Bis-(5-amidine-2-pyridyloxy)pentane, dihydrochloride, 88.
 $C_{17}H_{11}N_2Cl$ 2-Chloro-4- γ -diethylaminopropylamino-3-methylquinoline, and its dipicrate, 908.
 $C_{17}H_{11}N_2Cl$ 4-*p*-Chloroanilino-6- γ -dimethylaminopropylamino-2:5-dimethylpyrimidine, and its dihydrochloride, 1359.
 $C_{17}H_{11}ON$ 2-Keto-1-methyl-1- β -diethylaminoethyl-1:2:3:4-tetrahydronaphthalene, 401.
 $C_{17}H_{11}ON$ 4- γ -Diethylaminopropylamino-2-hydroxy-3-methylquinoline, 908.
 $C_{17}H_{11}ON$ 2-Amino-4- γ -diethylaminopropylamino-5-phenoxy-pyrimidine, 46.
 $C_{17}H_{11}N_2Cl$ 2-Amino-4-*p*-chloroanilino-6-diethylaminopropylamino-pyrimidine, 1363.
 $C_{17}H_{11}N_2Cl$ 2-Amino-4-*p*-chloroanilino-6-dimethylaminopropylamino-5-ethylpyrimidine, 1363.
 $C_{17}H_{11}ON$ 2-*p*-Chloroanilino-6- γ -diethylaminopropylamino-4-methyl-1:3:5-triazine, 158.
 $C_{17}H_{11}ON$ 2-Amino-4-*p*-anisidino-6-diethylaminoethylaminopyrimidine, 1363.
 $C_{17}H_{11}O_2N$ Undecanal 2:4-dinitrophenylhydrazone, 199.
 $C_{17}H_{11}P$ *p*-Ethylphenylmethyl dimethyl- β -allylphosphonium iodide, 1449.
 $C_{17}H_{11}P$ *p*-Xylylmethyl di- β -methylallylphosphonium iodide, 1449.
 $C_{17}H_{11}ON$ 5-Phenylureidodecane, 1496.
 $C_{17}H_{11}N_2Cl$ 4-Chloro-2- γ -di-*n*-butylaminopropylamino-5:6-dimethylpyrimidine, dipicrate, 48.
 $C_{17}H_{11}ON$ 2- γ -Di-*n*-butylaminopropylamino-4-hydroxy-5:6-dimethylpyrimidine, and its dipicrate, 48.
 $C_{17}H_{11}ON$ 2-Ureido-3-methylpentadecane, 1499.

17 IV

- $C_{17}H_{11}ONS$ 3-Hydroxy-2:2'-quinolythionaphthen, 1577.
 $C_{17}H_{11}ON_2Cl$ 8-Chloro-2-methyl-3:4:2':3'-pyridoaacridone, 681.
 $C_{17}H_{11}ON_2Br$ Acetyl-7-bromoquinoline, 610.
 $C_{17}H_{11}O_2NBr$ *cis*-4-Bromo-4'-cyano-2-methylstilbene- α -carboxylic acid, 691.
 $C_{17}H_{11}ONS$ 6-(2-Carboxyethyl)thionaphthindole, 658.
 $C_{17}H_{11}O_2NF$ Fluoro-5-diacetamidooacridines, 762.
 $C_{17}H_{11}O_2NS$ Diacetamidothioxanthone, 1233.
 $C_{17}H_{11}O_2NS$ *p*-Nitrophenyl 2-acetamido-4-phenyl-5-thiazyl sulphide, 118.
 $C_{17}H_{11}O_2NBr$ Toluene-*p*-sulphon-1-bromo-7-nitro-2-naphthalide, 330.
 $C_{17}H_{11}O_2NCl$ Methyl 2-(2':6'-dichloro-4'-nitrophenylamino)isoindolinone-3-acetate, 472.
 $C_{17}H_{11}O_2NBr$ Methyl 2-(2':6'-dibromo-4'-nitrophenylamino)isoindolinone-3-acetate, 473.
 $C_{17}H_{11}O_2NS$ *p*-Nitrophenyl 2-acetamido-4-phenyl-5-thiazyl sulphone, 118.
 $C_{17}H_{11}O_2NS$ 1:7-Dinitro-*p*-toluenesulphon-2-naphthalide, 1061.
 $C_{17}H_{11}ONCl$ 2-*p*-Chloroanilino-4-phenoxy-6-methylpyrimidine, 790.
 $C_{17}H_{11}ONCl$ Methyl-2-chloroethyl-2-acetoxyethylamine, and its salts, 517.
 $C_{17}H_{11}O_2NS$ Toluene-*p*-sulphon-6-nitro-2-naphthalide, 330.
 $C_{17}H_{11}O_2NCl$ Toluene-*p*-sulphon-7-nitro-2-naphthalide, 330.
 $C_{17}H_{11}O_2NCl$ Methyl 2-(2'-chloro-4'-nitrophenylamino)isoindolinone-3-acetate, 471.
 $C_{17}H_{11}O_2NBr$ Methyl 2-(2'-bromo-4'-nitrophenylamino)isoindolinone-3-acetate, 473.
 $C_{17}H_{11}O_2NS$ 4-(*p*-Nitrobenzenesulphonamido)-2-phenyl-6-methyl-3-pyridasone, 552.
 $C_{17}H_{11}NClS$ 10-Chloro-12-methyl-6-ethylthionaphthindole, and its picrate, 657.

- $C_{17}H_{13}O_2N_2Br$ 3-Nitro-2-phenyl-1-*p*-bromophenyl-*n*-butyl cyanide, 1508.
 $C_{17}H_{14}O_2N_2S$ 4-Sulphanilamido-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone, 553.
 $C_{17}H_{13}O_6N_3S$ 3-(4'-Nitro-2'-methoxyphenyl)-3:4-dihydrophthalazine-1-sulphonic-4-acetic acid, sodium salt, 463.
 $C_{17}H_{15}N_3ClS$ 5-Chloro-3-ethyl-2-aniloethylidenebenzthiazoline, 957.
 $C_{17}H_{16}O_2N_2Cl$ 2-Chloro-4:6-di-*p*-anisidino-1:3:5-triazine, 159.
 $C_{17}H_{16}O_2N_2S$ 4-Sulphanilamido-2-phenyl-6-methyl-3-pyridazone, 552.
 $C_{17}H_{16}O_2N_2S$ Ethyl hydroxyacetoxy-3-*p*-nitrophenylthio-2-methylpyridine-5-carboxylate, 54.
 $C_{17}H_{16}O_2N_2Cl$ 4'-Nitro-1:2'-dimethoxy-3-phenyl-4-methylphthalazinium perchlorate, 467.
 $C_{17}H_{16}O_2N_2S$ 5-Chloro-2-β-anilinoethylbenzthiazole ethochloride, 957.
 $C_{17}H_{17}O_2NS$ 4-Ethylacetamido-2'-carboxydiphenyl sulphide, 1232.
 $C_{17}H_{17}O_2N_2S$ Dimethyl-2-benzoyloxyethylsulphonium picrate, 769.
 $C_{17}H_{17}N_3ClSe$ 2-β-Anilinoethylbenzselenzazole ethochloride, 958.
 $C_{17}H_{17}N_3ISe$ 2-β-Anilinoethylbenzselenzazole ethiodide, 958.
 $C_{17}H_{17}Cl_2Br_2As$ 5-Chloro-2-[4 (or 5)-chloro-2-bromomethylbenzyl]-2-methylisoarsindolinium bromide, 669.
 $C_{17}H_{18}O_2NCl$ 2-Chloroethyl *N*-dibenzylcarbamate, 179.
 $C_{17}H_{18}O_2N_2S$ β-Benzylthio-*n*-butaldehyde dinitrophenylhydrazine, 1611.
 $C_{17}H_{18}O_2NS$ 4-Dimethylamino-2'-carbethoxydiphenyl sulphide, 1232.
 $C_{17}H_{20}O_2N_2S$ *N*'-Acetylsulphanilhomovanillylamide, 616.
 $C_{17}H_{20}O_2N_2P$ Adenosine-5'-benzyl phosphate, and its silver salt, 651.
 $C_{17}H_{23}O_2N_2Cl$ 4-γ-Diethylaminopropylamino-5-*p*-chlorobenzeneazo-2:6-dihydroxypyrimidine, and its dipicrate, 731.
 $C_{17}H_{23}N_3IS_2$ Bis-2-(4-methyl-3-ethylthiazole)pentamethincyanine iodide, 1443.
 $C_{17}H_{23}N_3ClS$ 2-β-Diethylaminoethylamino-4-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 $C_{17}H_{23}N_3S$ 4-β-Diethylaminoethylamino-2-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 $C_{17}H_{24}ONBr$ 9-Keto-5-methyl-2-ethyl-6:7-benzomorphan ethobromide, 401.
 $C_{17}H_{23}N_3IS_3$ [Bis-2-(3-methyl-Δ³-thiazoline)][αβ'-dimethin-2'-(3'-methyl-Δ²-thiazoline)]trimethincyanine di-iodide, 1442.

17 V

- $C_{17}H_{16}N_2ClHS$ 5-Chloro-2-β-anilinoethylbenzthiazole ethiodide, 957.

C₁₈ Group.

- $C_{18}H_{12}O_2$ Diketophenyl-α- and -β-naphthylethanes, 60.
 $C_{18}H_{12}N_2$ 9-(3'-Pyridyl)phenanthridine, and its salts, 1413.
 $C_{18}H_{13}N_2$ 3- and 7-Amino-9-(3'-pyridyl)phenanthridines, and their salts, 1415.
 $C_{18}H_{14}O_3$ Phenyl-α- and -β-naphthylglycollic acids, 60.
 $C_{18}H_{14}N_2$ *cis*- and *trans*-4:4'-Dicyano-2:2'-dimethylstilbenes, 692.
 $C_{18}H_{15}N_3$ *N,N*-Diphenylpicolinamide, and its picrate, 1116.
 $C_{18}H_{16}O_2$ 2':5-Dimethoxy-1-phenylnaphthalene, 226.
 $C_{18}H_{16}O_4$ 4'-Hydroxy-3:5:7-trimethoxyflavone, 123.
 $C_{18}H_{16}N_2$ 1-Methyl-2-aniloethylidenedihydroquinoline, 958.
 $C_{18}H_{16}N_2$ 1-Anilino-5-anilomethyl-1:3-pentadienes, hydrobromides, 961.
 $C_{18}H_{16}N_4$ 4:4'-Bis-(2-dihydroglyoxalinyldiphenyl, and its toluene-*p*-sulphonate, 500.
 $C_{18}H_{20}O_3$ Ethyl β-hydroxy-αγ-diphenylbutyrate, 1698.
 $C_{18}H_{20}O_5$ β-Hydroxy-αγ-di-*p*-methoxyphenylbutyric acid, 1698.
 $C_{18}H_{20}N_4$ *trans*-4:4'-Diamidino-2:2'-dimethylstilbene, dihydrochloride, 692.
 $C_{18}H_{21}N_3$ 2-Amino-8-diethylamino-3-methylacridine, 249.
 $C_{18}H_{22}N_4$ 2-(2-Diethylaminoethylamino)-*p*-phenanthroline, hydrobromide, 1661.
 $C_{18}H_{24}N_2$ *NN'*-Diphenyl-*N*-methyl-*N'*-ethyltrimethylenediamine, 311.
 $C_{18}H_{24}N_6$ 2-β-Diethylaminoethylamino-5-benzeneazo-4:6-dimethylpyrimidine, 51.
 $C_{18}H_{32}O_2$ Ricinoleic acid, scission of, 753.
 $C_{18}H_{24}N$ Di-*n*-octylacetoneitrile, 741.
 $C_{18}H_{23}N_7$ 2-Amino-4:6-bis-(γ-diethylaminopropylamino)pyrimidine, 47.
 $C_{18}H_{28}N_2$ αα-Diethyl-α-*n*-butylacet-*N*-*sec*-octylamide, 741.
 $C_{18}H_{28}N_2$ αα-Di-*n*-octylacetamide, hydrochloride, 741.
 $C_{18}H_{28}N_2$ Stearamidine, and its salts, 741.
 $C_{18}H_{29}N$ Di-*n*-nonylamine, and its salts, 199.
 $C_{18}H_{29}N$ Ethyldi-*n*-octylamine, 200.
 $C_{18}H_{29}N$ Hexadecylethylamine, hydrochloride, 199.
 $C_{18}H_{29}N$ Tri-*n*-hexylamine, oxalate, 200.

18 III

- $C_{18}H_{11}O_2N_3$ Nitro-9-(3'-pyridyl)phenanthridines, and their salts, 1414.
 $C_{18}H_{11}NS$ 10:11-Benzthionaphthindole, 657.
 $C_{18}H_{11}NS$ 11:12-Benzthionaphthindole, and its picrate, 657.
 $C_{18}H_{12}O_2N$ 7-Nitro-1-*p*-nitrobenzeneazo-2-naphthyl acetate, 1061.
 $C_{18}H_{12}Cl_2Sb$ Trichlorophenylstilbines, 1569, 1570.
 $C_{18}H_{12}Cl_2Sb$ Tri-*p*-chlorophenylstilbine dichloride, 1570.
 $C_{18}H_{12}Br_2Sb$ Tri-*p*-bromophenylstilbine dibromide, 1570.
 $C_{18}H_{13}O_2N$ α- and β-Naphthyl isonitrosobenzyl ketones, 60.
 $C_{18}H_{13}O_2N$ *N*-ω-Difurfurylidene-*p*-aminoacetophenone, 1420.
 $C_{18}H_{13}O_2N_3$ Nitro-2-nicotinamidodiphenyls, 1413.
 $C_{18}H_{13}ON$ 2-Nicotinamidodiphenyl, 1413.
 $C_{18}H_{13}O_2N_4$ 2:5-Diketo-3-(2'-nitro-4'-acetamidophenyl)isodolinopyrazolidocoline, 833.
 $C_{18}H_{14}N_2S_2$ Schiff's base, from 5-amino-2-mercapto-4-phenylthiazole, 1603.
 $C_{18}H_{14}N_2S_4$ 1':5-Bis-(2:4-dithio-5-phenylhydantoin), 1606.
 $C_{18}H_{14}ON$ 3-Methyl-3-(2'-benzoylviny)indole, 1631.

- $C_{10}H_7O_2N$ 2-Hydroxy-1-naphthaldehyde *p*-methoxyanil, 978.
 $C_{10}H_7O_2N$ 2:5-Diketo-3-(4'-acetamidophenyl)isoindolinopyrazolidocoline, 471.
 $C_{10}H_7O_2N$ 1-Acetoxy-3-(3'-nitrophenyl)-3:4-dihydrophthalazine-4-acetic acid, 473.
 $C_{10}H_7O_2Cl$ 1:1:1-Trichloro-2:2-di(4- ω -carboxymethoxyphenyl)ethane, 849.
 $C_{10}H_7O_2N$ Acetyl derivative of 1-hydroxy-3-(2':4'-diaminophenyl)-3:4-dihydrophthalazine-4-acetic acid lactam, 834.
 $C_{10}H_7O_2N$ Ethyl 2-(2':4'-dinitrophenylamino)isoindolinone-3-acetate, 832.
 $C_{10}H_7O_2N$ Ethyl 1-hydroxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine-4-acetate, 833.
 $C_{10}H_7O_2N$ Methyl 2-(2':4'-dinitrophenylmethylamino)isoindolinone-3-acetate, 833.
 $C_{10}H_7O_2N$ Methyl 1-keto-3-(2':4'-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetate, 834.
 $C_{10}H_7O_2N$ Acetyl-2:7-diamino-9-methylphenanthridine, 72.
 $C_{10}H_7O_2N$ Methyl *N*-benzoyl-1:2:3:4-tetrahydroisoquinolinate, 129.
 $C_{10}H_7O_2N$ 4'-Acetamido-2'-methoxy-3-phenyl-1-methylphthalaz-1-one, 467.
 $C_{10}H_7O_2N$ 4'-Acetamido-2'-methoxy-3-phenyl-4-methylphthalaz-1-one, 467.
 $C_{10}H_7O_2N$ Methyl 2-(4'-nitro-2'-methylphenylamino)isoindolinone-3-acetate, 473.
 $C_{10}H_7O_2N$ 2:6-Dimethyl galactonamide, 1625.
 $C_{10}H_7O_2N$ 1-Keto-3-(4'-nitro-2'-methoxyphenyl)-2-methyltetrahydrophthalazine-4-acetic acid, 464.
 $C_{10}H_7O_2N$ Methyl 1-hydroxy-3-(4'-nitro-2'-methoxyphenyl)-3:4-dihydrophthalazine-4-acetate, 464.
 $C_{10}H_7O_2N$ Methyl 2-(4'-nitro-2'-methoxyphenylamino)isoindolinone-3-acetate, 465.
 $C_{10}H_7O_2N$ 4'-Acetamido-2'-methoxy-*N*-phenyl-3-methylphthalimidine, 468.
 $C_{10}H_7O_2N$ 4:4'-Diacetamidobenzoin, 251.
 $C_{10}H_7O_2N$ *O*-Carbethoxyhomovanillin 2:4-dinitrophenylhydrazine, 1694.
 $C_{10}H_7N_2S$ 3-Ethyl-2- β -anilopropylidenebenzthiazoline, 958.
 $C_{10}H_7N_2S$ 3-Ethyl-2-aniloisopropylidenebenzthiazoline, 958.
 $C_{10}H_7OP$ *p*-Phenoxyphenyldiallylphosphine, 1448.
 $C_{10}H_7O_2N$ *O*-Carbethoxyhomovanillin *p*-nitrophenylhydrazine, 1694.
 $C_{10}H_7O_2N$ *s*-Bisphenylacetoehtylenediamide, 503.
 $C_{10}H_7O_2N$ Bis-(2:4-dinitrophenyl)-2-methylpentane, 1398.
 $C_{10}H_7ON$ ω -Dimethylamino- ω - α -phenylethylacetophenones, and their picrates, 94.
 $C_{10}H_7ON$ 1-*cis*- and -*trans*-3-Methylcyclohexyl- α -naphthylurethanes, 206, 207.
 $C_{10}H_7ON$ 5-Benzamidomethyl dihydroeugenol, 126.
 $C_{10}H_7ON$ Dimethylaminoethyl benzilate, 60.
 $C_{10}H_7ON$ 2-Amino-4:4'-dicarbethoxyaminodiphenyl, 71.
 $C_{10}H_7ON$ 3-Diethylaminophenol *N*-benzylurethane, and its methiodide, 189.
 $C_{10}H_7ON$ Bis-(*m*-dimethylamino)oxanilide, 247.
 $C_{10}H_7ON$ Methyl 1-triacetyl-*d*-xylosidoglyoxaline-4:5-dicarboxylate, 380.
 $C_{10}H_7ON$ 2- γ -Diethylaminopropylamino-4-hydroxy-1:3-diaza-acridine, and its salts, 734.
 $C_{10}H_7ON$ 2-Acetamido 2-acetyl 4:6-benzylidene α -methylaltroside, 20.
 $C_{10}H_7ON$ 2-Acetamido 3-acetyl 4:6-benzylidene α -methylglucoside, 21.
 $C_{10}H_7ON$ 4-Hydroxy-5-, 6-, 7-, and 8-methoxy-3-*n*-heptylquinolines, 1038.
 $C_{10}H_7OP$ Tri- β -methylallylphosphine-*p*-benzoquinone, 1449.
 $C_{10}H_7ON$ Ethyl 2-*o*-anisidino-5-ethylcyclohex-1-enecarboxylate, 1038.
 $C_{10}H_7ON$ Ethyl *N*-benzoyl-4-propylpiperidine-2-carboxylate, 223.
 $C_{10}H_7ON$ Ethyl β -(3:4-diethylcarbonatophenyl)-*N*-methylserine, salts, 661.
 $C_{10}H_7ON$ 10-Benzamidodecyl cyanide, 1371.
 $C_{10}H_7ON$ 2- β -Diethylaminoethylamino-4-*p*-methoxyphenoxy-6-methylpyrimidine, 789.
 $C_{10}H_7ON$ 4-*p*-Nitroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine, and its dihydrochloride, 1350.
 $C_{10}H_7ON$ 2-Nitro-3-diethylaminobutane, 1488.
 $C_{10}H_7ON$ 2-Chloro-4- γ -diethylaminopropylamino-3-ethylquinoline, and its dipicrate, 909.
 $C_{10}H_7ON$ 4-*p*-Chloroanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine, and its dihydrochloride, 1358.
 $C_{10}H_7ON$ 4-*p*-Chloroanilino-6- γ -dimethylaminopropylamino-2-methyl-5-ethylpyrimidine, and its salts, 1360.
 $C_{10}H_7ON$ 4-*p*-Bromoanilino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine, 1359.
 $C_{10}H_7ON$ 4- γ -Diethylaminopropylamino-2-hydroxy-3-ethylquinoline, 908.
 $C_{10}H_7ON$ 4- γ -Diethylaminopropylamino-6-methoxyquinoline, dihydrochloride, 1553.
 $C_{10}H_7ON$ Ethyl *N*-benzyl-4-propylpiperidine-2-carboxylate, 224.
 $C_{10}H_7ON$ Ethyl 3-(2-benzamidoehtyl)hexane-1-carboxylate, 223.
 $C_{10}H_7ON$ 2-Amino-4-*p*-chloroanilino-6-diethylaminoethylamino-5-ethylpyrimidine, 1363.
 $C_{10}H_7ON$ 5-Acetamido-3- β -diethylaminoethylamino-*o*-xylene, 912.
 $C_{10}H_7ON$ *N,N'*-Dimethylhexamethylenediamine-*N*-carboxydiethylamide-*N'*-carboxymorpholide, 318.
 $C_{10}H_7ON$ *N,N'*-Dimethylhexamethylenediamine-*N,N'*-biscarboxydiethylamide, 315.

18 IV

- $C_{10}H_7ON_2S$ 6-Nitroso-11:12-benzthionaphthindole, 658.
 $C_{10}H_7ON_2S$ 2-Nitro-11:12-benzthionaphthindole, 657.
 $C_{10}H_7ON_2S$ Benzthioindoxyl 2:4-dinitrophenylhydrazones, 658.
 $C_{10}H_7Cl_2Br_2Sb$ Tri-*p*-bromophenylstibine dichloride, 1570.
 $C_{10}H_7Cl_2Br_2Sb$ Tri-*p*-chlorophenylstibine dibromide, 1570.
 $C_{10}H_7Cl_2I_2Sb$ Tri-*p*-chlorophenylstibine diiodide, 1570.
 $C_{10}H_7Br_3ISb$ Tri-*p*-bromophenylstibine diiodide, 1570.
 $C_{10}H_7Cl_3As$ Phenyl-*p*-chlorophenyl-*p*-bromophenylarsine, and its hydroxy-picrate, 511.
 $C_{10}H_7ON_2S$ 2-Dibenzamido-4-mercaptopomethylthiazole, 324.
 $C_{10}H_7ON_2S$ *N*-Benzoylbenzenesulphon-2-pyridylamide, 387.
 $C_{10}H_7ON_2Cl$ 2:5-Diketo-3-(2'-chloro-4'-acetamidophenyl)isoindolinopyrazolidocoline, 472.
 $C_{10}H_7ON_2Cl$ Ethyl 8'-chloro-6'-quinolyanthranilate, 680.
 $C_{10}H_7ON_2S$ 5-Acetamido-4-*p*-nitrobenzenazo-2-benzylthiazole, 1597.
 $C_{10}H_7ON_2Br$ 7-Carbethoxyamino-9:10-dimethylphenanthridinium bromide, 71.

- $C_{12}H_{11}N_2IS$ 2-(β -Anilino- α -methylvinyl)benzthiazole ethiodide, 958.
 2-(β -Anilino- β -methylvinyl)benzthiazole ethiodide, 958.
 $C_{12}H_{10}O_2N_2S$ β -Benzylthioisovaleraldehyde dinitrophenylhydrazone, 1611.
 $C_{19}H_{20}O_2NS$ 7-Acetamido-9-methylphenanthridine methosulphate, 71.
 $C_{12}H_{11}O_2NS_2$ 2-Ethylbenzthiazole etho-*p*-toluenesulphonate, 958.
 $C_{12}H_{13}ONBr$ *l*-Phenacyl- α -phenylethyldimethylammonium bromide, rearrangement of, 93.
 $C_{12}H_{13}O_2N_2S$ N^4 -Acetylsulphanil- α -vanillylethylamide, 616.
 $C_{12}H_{12}N_4OS$ 2- γ -Diethylaminopropylamino-4-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 4- γ -Diethylaminopropylamino-2-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 4- γ -Diethylaminopropylamino-6-*p*-chlorophenylthio-2-methylpyrimidine, 789.
 $C_{12}H_{13}ON_2S$ 2- β -Diethylaminoethylamino-4-*p*-methoxyphenylthio-6-methylpyrimidine, 788.
 4- β -Diethylaminoethylamino-2-*p*-methoxyphenylthio-6-methylpyrimidine, 788.
 $C_{12}H_{21}N_3IS_2$ Bis-2-(3-ethyl- Δ^4 -thiazoline)- δ -methylheptamethincyanine iodide, 962.
 $C_{12}H_{20}ON_2S$ 11-Benzamidothioundecamide, 1377.

18 V

- $C_{11}H_{11}OCIBrAs$ Phenyl-*p*-chlorophenyl-*p*-bromophenylarsino oxide, 511.
 $C_{12}H_{11}ONBrMg$ Substance, from action of Grignard reagents on 3-acetyl-2-phenylpyrrocoline, 672.
 $C_{12}H_{21}O_2N_2IS$ 4-Methyl-5-carbethoxymethylthiazole-2-aldehyde *p*-dimethylaminoanil methiodide, 1402.

 C_{19} Group.

- $C_{19}H_{19}O_3$ 2'-Methoxy-1:2-benzanthraquinone, 942.
 $C_{19}H_{17}O$ 2'-Methoxy-1:2-benzanthracene, and its picrate, 942.
 $C_{19}H_{17}O$ 1':5-Dimethoxy-3:4-benzfluorenone, 226.
 1-*p*-Toluoylnaphthalene-2-carboxylic acid, 765.
 $C_{19}H_{17}O_2$ 2-(2'-Methoxybenzoyl)-1-naphthoic acid, 942.
 $C_{19}H_{17}O_2$ 1-*p*-Methylbenzyl-naphthalene-2-carboxylic acid, 765.
 $C_{19}H_{17}O_4$ 2':5-Dimethoxy-1-phenylnaphthalene-2 (or 3)-carboxylic acid, 226.
 $C_{19}H_{17}O_2$ Acetoxyanhydroacetylavanicin, 1028.
 $C_{19}H_{17}O_3$ Diacetylavanicin, 1027.
 $C_{19}H_{21}N_3$ 1-Anilino-5-anilo-1:5-dimethyl-1:3-pentadiene, hydrochloride, 961.
 1:3:3-Trimethyl-2-aniloethylideneindoline, 959.
 $C_{19}H_{21}N_4$ 2-(3-Diethylaminopropylamino)-*p*-phenanthroline, hydrobromide, 1661.
 $C_{19}H_{21}N_4$ 2-Amino-4-*p*-cyanoanilino-6-diethylaminoethylamino-5-ethylpyrimidine, 1363.
 $C_{19}H_{23}O_3$ 3(β):6(β):Dihydroxyætiocolan-17-one, 814.
 $C_{19}H_{23}N$ Benzyl-di-*n*-hexylamine, oxalate, 200.
 $C_{19}H_{27}N$ Methyl-di-*n*-nonylamine, hydrochloride, 200.
n-Propyl-di-*n*-octylamine, 200.

19 III

- $C_{19}H_{11}O_2N_2$ 4-Nitro-2'-o-nitrobenzamidodiphenyl, 73.
 $C_{19}H_{11}NBr_2$ 2-Bromo-9-*p*-bromophenylphenanthridine, 86.
 $C_{19}H_{15}O_2N_4$ 3:5':3':5'-Tetracyano- α -*p*-diphenoxypropane, 83.
 $C_{19}H_{11}N_4Cl$ 4-Chloro-2-*p*-chloroanilino-7:8-benzoquinoline, 906.
 $C_{19}H_{13}O_2N_2$ 7-Amino-9-o-nitrophenylphenanthridine, 73.
 7-Amino-9-*p*-nitrophenylphenanthridine, 72.
 $C_{19}H_{13}O_2N_3$ 3-Nitro-9-(6'-keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine, and its hydrochloride, 1414.
 $C_{19}H_{15}O_2Cl$ 2-Phenyl- β -naphthopyrylium perchlorate, 348.
 $C_{19}H_{13}NS$ 2-Methyl-11:12-benzthionaphthindole, and its picrate, 657.
 6-Methyl-11:12-benzthionaphthindole, and its dipicrate, 657.
 $C_{19}H_{15}ON_2$ 9-(6'-Keto-1'-methyl-1':6'-dihydro-3'-pyridyl)phenanthridine, and its salts, 1414.
 $C_{19}H_{11}OSb$ 10-Phenyl-2-methylphenoxstibine, 7.
 $C_{19}H_{11}OS$ 2-Phenyl-6'-ethoxythionaphtheno(2':3':5:6'-pyrylium hydroxide, salts, 349.
 $C_{19}H_{15}N_2S_2$ 5:5-Di-*n*-propyl-2:4-dithiohydantoin, 683.
 $C_{19}H_{15}ClAs$ Phenyl-*p*-tolyl-*p*-chlorophenylarsine, and its hydroxy-picrate, 509.
 $C_{19}H_{17}ON$ 2-Hydroxy-1-naphthylmethylene-*o*-3-xyldine, 1047.
 5-Phenoxytetrahydroacridine, 636.
 $C_{19}H_{17}O_2N$ 1-Benzoyl-6-acetyl-2:3-dimethylindole, 1633.
 12-Phenoxy-9-methoxy-2:3-dihydro- β -quinindene, 636.
 $C_{19}H_{17}O_2N_2$ *O*-Acetoxy-3-(4'-nitro-2'-methoxyphenyl)-3:4-dihydrophthalazine-4-acetic acid, 464.
 $C_{19}H_{15}O_2N_4$ 3:4-Diethylcarbonatobenzaldehyde 2:4-dinitrophenylhydrazone, 660.
 $C_{19}H_{17}O_2N_2$ 2:7-Diacetamido-9:10-dimethylphenanthridine, hydrochloride, 72.
 2-Methylamino-4:6-dibenzyloxy-pyrimidine, 732.
 4-Methylamino-2:6-dibenzyloxy-pyrimidine, 732.
 $C_{19}H_{17}O_2N_4$ 4-Guanidino-2:6-dibenzyloxy-pyrimidine, and its picrate, 733.
 $C_{19}H_{17}O_2N_2$ Ethyl 1-hydroxy-3-(4'-nitro-2'-methoxyphenyl)-3:4-dihydrophthalazine-4-acetate, 464.
 Methyl 1-keto-3-(4'-nitro-2'-methoxyphenyl)-2-methyltetrahydrophthalazine-4-acetate, 464.
 $C_{19}H_{17}N_2S$ 3-Methyl-2-dianiloisopropylidenethiazolidine, 1440.
 $C_{19}H_{17}ON_2$ Ethyl anilinoanillylcyanacetate, 617.
 $C_{19}H_{17}ON_2$ 5-Cyano-3:3':5'-triamidino- α -*p*-diphenoxypropane, hydrochloride, 83.
 $C_{19}H_{17}ON_2$ 2:4-Di-*p*-anisidino-6-ethoxy-1:3:5-triazine, hydrochloride, 160.
 $C_{19}H_{17}ON$ 1-Phenylcarbamyl-2:3-dimethyl-6-ethylindoline, 1633.
 $C_{19}H_{21}O_2$ 1:3-Dibenzamido-2:2-dimethylpropane, 1502.
 $C_{19}H_{21}O_2N_4$ 1-Tetra-acetyl-*d*-glucosidoglyoxaline-4:5-dicarboxamide, 380.
 $C_{19}H_{21}O_2N_4$ *n*-Propyl-*n*-butylcarbinyl α -naphthylurethane, 751.
 $C_{19}H_{21}N_4Cl$ *N*-*p*-Chlorophenyl-*N'*- β -diethylaminoethylaminophenylguanidines, 916.

- $C_{11}H_{12}O_2N_4$ 2- γ -Diethylaminopropylamino-4-*p*-methoxyphenoxy-6-methylpyrimidine, and its dipicrate, 789.
 $C_{11}H_{12}N_4Cl$ 4-*p*-Chloroanilino-6- β -diethylaminoethylamino-2-methyl-5-ethylpyrimidine, and its dihydrochloride, 1360.
 4-*p*-Chloroanilino-6- γ -diethylaminopropylamino-2:5-dimethylpyrimidine, and its dihydrochloride, 1359.
 $C_{11}H_{12}ON_4$ 4-*p*-Anisidino-6- β -diethylaminoethylamino-2:5-dimethylpyrimidine, and its dihydrochloride, 1359.
 4-*p*-Anisidino-6- γ -dimethylaminopropylamino-2-methyl-5-ethylpyrimidine, 1361.
 $C_{11}H_{12}N_4Cl$ 2-Amino-4-*p*-chloroanilino-6-diethylaminopropylamino-5-ethylpyrimidine, 1363.
 $C_{11}H_{12}O_2N_4$ *l*-trans-3-Methylcyclohexyl *l*-menthylaminoacetate, sulphate of, 207.
 $C_{11}H_{18}O_2N_4$ *NN'*-Di-(2-ethoxyethyl)ethylenediamine-*N*-carboxydimethylamide-*N'*-carboxypiperidine, 318.
 $C_{10}H_{18}ON$ 1-Acetamidoheptadecane, 199.

19 IV

- $C_{10}H_{11}ONCl_2$ 3:6-Dichloro-9-benzoylcarbazole, 939.
 $C_{10}H_{11}O_2NCl$ 2-*p*-Chloroanilino-2-hydroxyperinaphthindane-1:3-dione, 130.
 $C_{10}H_{11}ONBr_2$ 5-Bromo-2-*p*-bromobenzamidodiphenyl, 86.
 $C_{10}H_{11}O_2NS$ 3-Acetoxy-2-2'-quinolythionaphthen, 1577.
 $C_{10}H_{11}ONBr$ 2-*p*-Bromobenzamidodiphenyl, 86.
 $C_{10}H_{11}OBrSb$ 10-*p*-Bromophenyl-2-methylphenoxstibine, 8.
 $C_{10}H_{11}OClSb$ 10-Phenyl-2-methylphenoxstibine dichloride, 7.
 $C_{10}H_{11}OClAs$ Phenyl-*p*-tolyl-*p*-chlorophenylarsine oxide, 509.
 $C_{10}H_{11}O_2N_2S$ 4-Amino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide, perchlorate, 1232.
 $C_{10}H_{11}O_2N_2Cl$ Ethyl 4-chloro-(8'-methyl-6'-quinolyl)anthranilate, 681.
 $C_{10}H_{11}O_2N_2S$ 4-(*N*-Acetylulphanilamido)-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone, 553.
 $C_{10}H_{11}O_2N_2S$ 4-(*N*-Acetylulphanilamido)-2-phenyl-6-methyl-3-pyridazone, 552.
 $C_{10}H_{11}O_2N_2S$ Ethyl 4:6-diacetoxy-3-*p*-nitrophenylthio-2-methylpyridine-5-carboxylate, 54.
 $C_{10}H_{11}O_2NS$ 3-(2'-*p*-Toluenesulphonylcarbamyphenyl-1'-thio)pentane-2:4-dione, 1576.
 $C_{10}H_{11}N_2S$ Bis-2-(3-ethyl- Δ^2 -thiazoline)- $\beta\beta$ -dimethylheptamethincyanine iodide, 962.
 $C_{10}H_{11}O_2N_2S$ 5-*n*-Hexamido-4-carbethoxy-2-benzylthiazole, hydrochloride, 1596.
 $C_{10}H_{12}ON_2S$ 2- γ -Diethylaminopropylamino-4-*p*-methoxyphenylthio-6-methylpyrimidine, 788.
 4- γ -Diethylaminopropylamino-2-*p*-methoxyphenylthio-6-methylpyrimidine, 788.
 $C_{10}H_{12}O_3N_2S$ 10-(*p*-Acetamidobenzenesulphonamido)decyl cyanide, 1371.

 C_{20} Group.

- $C_{20}H_{14}O_4$ 2':5-Dimethoxy-1-phenylnaphthalene-2:3-dicarboxylic anhydride, 226.
 $C_{20}H_{14}N_2$ 1:1'-Azonaphthalene, reduction of, 77.
 $C_{20}H_{16}O$ 9-*m*-Tolylxanthen, 1000.
 $C_{20}H_{16}O_2$ 9-*m*-Tolylxanthhydrol, 1000.
 $C_{20}H_{16}N_2$ Bis-2-(5-phenylpyrrole)azamethin, salts, 1200.
 $C_{20}H_{16}O_4$ Methyl 2':5-dimethoxy-1-phenylnaphthalene-2(or 3)-carboxylate, 226.
 $C_{20}H_{16}O_4$ 2:5-Dibenzoyl 1:4:3:6-dianhydro-*d*-iditol, 1404.
 2:5-Dibenzoyl dianhydro-*l*-iditol, 1404.
 $C_{20}H_{16}O_7$ 4'-Acetoxy-3:5:7-trimethoxyflavone, 123.
 $C_{20}H_{17}N_3$ 7-Piperidino-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 $C_{20}H_{17}O_4$ 5:6-Dimethoxy-3-veratryl-2-methylhydrindone, 951.
 Ethyl $\alpha\beta$ -di-*p*-methoxyphenylacetacetate, 1698.
 4-Keto-6:7-dimethoxy-1-veratryl-1:2:3:4-tetrahydronaphthalene, 951.
 $C_{20}H_{16}O_4$ Diisocugenol, structure of, 948.
 5:6-Dimethoxy-3-veratryl-2-methylhydrindone, 951.
 6:7-Dimethoxy-1-veratryl-1:2:3:4-tetrahydronaphthalene, 951.
 $C_{20}H_{16}O_4$ $\beta\beta$ -Diveratryl- α -methylpropionic acid, 951.
 $C_{20}H_{16}Br_2$ 2:2'-Dibromo-3:4-di-*tert*-butylacenaphthene, 745.
 $C_{20}H_{16}Br$ 2-Bromo-3:4-di-*tert*-butylacenaphthene, 745.
 $C_{20}H_{16}N_4$ 4-(Quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidines, 1617, 1619.
 $C_{20}H_{17}N$ 2-Amino-3:4-di-*tert*-butylacenaphthene, 744.
 $C_{20}H_{17}N_2$ *NN'*-Diphenyl-*NN'*-diisopropylethylenediamine, 310.
 $C_{20}H_{18}S_2$ 5(or 2)-Mercapto-1:2:6-trimethylheptyl 4-methyl-1-isopropylhex-4-enyl sulphide or 1:5-dimethyl-1-ethylhex-4-enyl sulphide, 1539.
 $C_{20}H_{24}S_2$ Dihydromyrcene bis(*iso*amyl sulphide), 40.
 $C_{20}H_{43}N$ Di-*n*-decylamine, hydrochloride, 200.
 Ethyldi-*n*-nonylamine, hydrochloride, 200.

20 III

- $C_{20}H_{11}O_2N_4$ 3:6-Dinitro-1:2:7:8-dibenzocarbazole, 77.
 $C_{20}H_{11}NCl_2$ 3:6-Dichloro-1:2:7:8-dibenzocarbazole, 78.
 $C_{20}H_{11}O_2N_4$ 6-Nitronaphthalene-2:1'-azo-6'-nitro-2'-naphthol, 331.
 $C_{20}H_{11}O_2N_4$ 3:3'-Dinitro-4:4'-dihydroxy-1:1'-dinaphthyl, 1574.
 $C_{20}H_{11}N_2Br_2$ 1:1'-Dibromo-2:2'-azonaphthalene, 1392.
 $C_{20}H_{11}ON_2$ 3:4-Diphenylcinnoline *N*-oxide, 1651.
 3-Phenyl-4-*p*-hydroxyphenylcinnoline, 1651.
 $C_{20}H_{11}O_2N_4$ Bis-3-(2-keto-5-phenyl-2:3-dihydropyrrolylidene), 1199.
 $C_{20}H_{11}O_2N_4$ 3:3'-Dinitro-4:4'-diamino-1:1'-dinaphthyl, 1573.
 $C_{20}H_{11}N_2Cl_2$ 1:1'-Dichloro-2:2'-diamino-3:3'-dinaphthyl, and its dihydrochloride, 1391.
 $C_{20}H_{11}N_2Br_2$ 1:1'-Dibromo-2:2'-diamino-3:3'-dinaphthyl, and its dihydrochloride, 1392.
 $C_{20}H_{11}N_2Br$ 1-Bromo-2-naphthaleneazo- β -naphthylamine, 1391.
 $C_{20}H_{11}N_4Cl$ 2:4-Bis-*p*-chloroanilinoquinazoline, 760.

- $C_{20}H_{13}ON_8$ Acetamido-9-(3'-pyridyl)phenanthridines, 1415.
 $C_{20}H_{13}O_5Sb$ 10-*p*-Carboxyphenyl-2-methylphenoxstibine, 9.
 $C_{20}H_{15}ON$ 2':5-Dimethoxy-1-phenylnaphthalene-2:3-dicarboxyimide, 227.
 $C_{20}H_{11}O_2Cl$ 2-*m*-Methoxyphenyl- β -naphthopyrylium perchlorate, 1348.
 $C_{20}H_{16}ON_2$ 6-Nitro-1-hydrindenol β -naphthylurethane, 95.
 $C_{20}H_{17}ON$ 3:5-Diphenyl-2-(but-1'-en-3'-onyl)pyrrole, 1631.
 $C_{20}H_{16}ON_2$ Hex-2-en-4-yne-1:6-diyl bisphenylurethane, 1589.
 $C_{20}H_{16}N_3Cl$ 7-Amino-9-*o*-aminophenyl-10-methylphenanthridinium chloride, 74.
 $C_{20}H_{18}ClAs$ Di-*p*-tolyl-*p*-chlorophenylarsine, 513.
 $C_{20}H_{19}ON$ 3-(*o*-3-Xylidino)-4:5-benzocoumaran, 1047.
 $C_{20}H_{19}ON$ 3-(*m*-4-Xylidino)-4:5-benzocoumaran, 1047.
 $C_{20}H_{19}ON$ 3-(*p*-Xylidino)-4:5-benzocoumaran, 1047.
 $C_{20}H_{20}ON_2$ 5-Benzimido-1-benzoyl-2:2-dimethylpyrrolidine, 1510.
 $C_{20}H_{21}ON_2$ Non-2-en-4-yn-1-yl α -naphthylurethane, 1585.
 $C_{20}H_{21}ON_3$ 2-Dimethylamino-4:6-dibenzoyloxypyrimidine, and its picrate, 732.
 $C_{20}H_{21}ON_3$ 4-Dimethylamino-2:6-dibenzoyloxypyrimidine, 732.
 $C_{20}H_{21}O_2Br$ 2-Bromo-3:4-di-*tert*-.butylacenaphthenequinone, 745.
 $C_{20}H_{21}O_2Br$ 3-Bromo-4:5-di-*tert*-.butylnaphthalic anhydride, 745.
 $C_{20}H_{21}ON_3$ 2:7-Dicarbethoxyamino-9-methylphenanthridine, 71.
 $C_{20}H_{21}ON_3$ 3-Nitro-4:5-di-*tert*-.butylnaphthalic anhydride, 744.
 $C_{20}H_{21}N_2S$ 3-Ethyl-2-dianilinoisopropylidenethiazolidine, 1440.
 $C_{20}H_{22}ON_2$ 3-Nitro-4:5-di-*tert*-.butylnaphthalimide, 745.
 $C_{20}H_{22}ON_4$ *O*-Picryl-*N*-hexovanillylamide, 615.
 $C_{20}H_{23}NI$ 4-*p*-Dimethylaminostyryl-1-ethylcinnolinium iodide, 811.
 $C_{20}H_{23}ON_3$ 2-Phthalimido-3:6-di-*sec*-.butylpyrazine, 377.
 $C_{20}H_{23}ON_3$ 5:6-Dimethoxy-3-veratryl-2-methylhydrindone oxime, 951.
 $C_{20}H_{23}ON_3$ 2-Acetamido-4:4'-dicarbethoxyaminodiphenyl, 71.
 $C_{20}H_{24}ON_2$ 2:4-Dibenzamido-2-methylpentane, 1398.
 $C_{20}H_{24}ON_2$ *V.V.*-2:4-Dibenzamido-2-methylpentane, 1491.
 $C_{20}H_{24}ON_2$ 2:7-Dinitro-3:4-di-*tert*-.butylacenaphthene, 744.
 $C_{20}H_{25}ON_2$ 2-Nitro-3:4-di-*tert*-.butylacenaphthene, 744.
 $C_{20}H_{25}ON_2$ Diethylaminoethyl benzilate, 60.
 $C_{20}H_{25}ON_3$ 2-Phthalimido-3:6-di-*sec*-.butylpyrazine, 377.
 $C_{20}H_{25}O_2Br$ *p*-Bromophenacyl-1-cyclohexylpent-1-ene-1-carboxylate, 772.
 $C_{20}H_{25}ON_3$ ψ -Ionone 2:4-dinitrophenylsemicarbazone, 1390.
 $C_{20}H_{25}N_2Br$ 4-(5'-Bromo-8'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine, and its dihydrochloride, 1619.
 $C_{20}H_{26}ON_4$ Hexamethylenedibenzamidoxime, 968.
 $C_{20}H_{27}ON_2$ 2:9-Diketo-4-methyl-5- β -diethylaminoethyl-6:7-benzobicyclo[3:3:1]nonane, 400.
 $C_{20}H_{27}O_2Br$ *p*-Bromophenacyl-1-cyclohexylpentane-1-carboxylate, 772.
 $C_{20}H_{28}ON_3Cl$ 4'-Chloro-3- β -diethylaminoethylamino-4:5-dimethyldiphenylamine, and its di-*p*-toluenesulphonate, 913.
 $C_{20}H_{29}ON_4$ *N*-*p*-Methoxyphenyl-*N'*-*p*- β -diethylaminoethylaminophenylguanidine, 916.
 $C_{20}H_{30}ON_4$ 2-*n*-Heptylidene-*n*-heptaldehyde dinitrophenylhydrazone, 966.
 $C_{20}H_{30}ON_4Cl$ 4-*p*-Chloroanilino-6- β -diethylamino- α -methylbutylamino-2-methylpyrimidine, dipicrate, 1357.
 $C_{20}H_{30}ON_4$ 4-*p*-Chloroanilino-6- γ -diethylaminoethylamino-2-methyl-5-ethylpyrimidine, and its dihydrochloride, 1361.
 $C_{20}H_{31}ON_3$ 4- δ -Diethylamino- α -methylbutylamino-6-methoxyquinadine, and its dihydrobromide, 1553.
 $C_{20}H_{31}ON_3$ 4-*p*-Anisidino-6- β -diethylaminoethylamino-2-methyl-5-ethylpyrimidine, dihydrochloride, 1361.
 $C_{20}H_{31}N_2Cl_2$ 2-Chloro-4-*p*-chloroanilino-6- $\alpha\gamma$ -bisdiethylaminoisopropylamino-1:3:5-triazine, and its hydrochloride, 159.
 $C_{20}H_{33}N_3Cl$ 2-Amino-4-*p*-chloroanilino-6- $\alpha\gamma$ -bisdiethylaminoisopropylamino-1:3:5-triazine, 159.

20 IV

- $C_{20}H_{11}O_3NCl_2$ 3:6-Dichlorocarbazole-9-phthalolylic acid, 939.
 $C_{20}H_{13}ON_2Br$ 1-Bromo-2-naphthaleneazo- β -naphthol, 1391.
 $C_{20}H_{14}ONSb$ 10-*p*-Cyanophenyl-2-methylphenoxstibine, 8.
 $C_{20}H_{14}ON_3Cl$ 2-*p*-Chloroanilino-4-phenoxyquinazoline, 780.
 $C_{20}H_{14}ON_3S_2$ 2-Methylthio-4-phenylthiazole-5-azo- β -naphthol, 1604.
 $C_{20}H_{15}O_2Cl_2Fe$ 2-*m*-Methoxyphenyl- β -naphthopyrylium chloride, 348.
 $C_{20}H_{15}N_2Cl_2Br_2$ Bis-2-(5-*p*-bromophenylpyrrole)azamethin dihydrochloride, 1200.
 $C_{20}H_{15}ON_2Cl_2$ 4':4''-Dichloro-3-nitro-4:5-dimethyltriphenylamine, 913.
 $C_{20}H_{16}ON_2Cl$ 7-Amino-9-*o*-nitrophenyl-10-methylphenanthridinium chloride, 73.
 $C_{20}H_{16}ON_2Cl$ 7-Amino-9-*p*-nitrophenyl-10-methylphenanthridinium chloride, 73.
 $C_{20}H_{17}ON_2Cl$ α -Anilinothienylacet-*p*-chloroanilide, 1044.
 $C_{20}H_{17}ON_2Cl_2$ Bis-2-(5-hydroxyphenylpyrrole)azamethin dihydrochlorides, 1200.
 $C_{20}H_{17}O_2N_2S_2$ 4-Amino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide, and its perchlorate, 1232.
 $C_{20}H_{17}ON_2S$ 4-Methylamino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide, 1232.
 $C_{20}H_{17}O_2N_2S$ Sulphanilylvanill-*N'*-phenylamidine, 617.
 $C_{20}H_{18}ON_3S$ *N*-Phenyl-*p*-methylsulphonylbenzamidinium benzenesulphonate, 394.
 $C_{20}H_{18}N_2ClI$ 6- and 7-Chloro-4-*p*-dimethylaminostyryl-1-ethylcinnolinium iodides, 811.
 $C_{20}H_{18}ON_2Br$ 3-Bromo-4:5-di-*tert*-.butylnaphthalimide, 746.
 $C_{20}H_{18}ON_2S$ 9-Tetra-acetyl-*d*-mannopyranosido-2-methylthioadenine, 357.
 $C_{20}H_{18}ON_2Cl$ Methyl-*n*-propylaminoethyl benzilate hydrochloride, 60.
 $C_{20}H_{18}ON_2I$ Trimethyl-2-hydroxyethylammonium iodide *N*-dibenzylurethane, 180.
 $C_{20}H_{18}ON_2Cl$ 2- δ -Diethylamino- α -methylbutylamino-4-*p*-chlorophenoxy-6-methylpyrimidine, 789.
 $C_{20}H_{18}ON_2Cl$ 4- δ -Diethylamino- α -methylbutylamino-2-*p*-chlorophenoxy-6-methylpyrimidine, 788.

- $C_{20}H_{19}O_2BrS$ 2'(or 5')-Bromo-5-ethoxy-3':4'-di-*tert.*-butyl-1:7'-thionaphthenacenaphthenylindigo, 746.
 $C_{20}H_{19}N_2OS$ 2-8-Diethylamino- α -methylbutylamino-4-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 4- γ -Diethylamino- α -methylbutylamino-2-*p*-chlorophenylthio-6-methylpyrimidine, 788.
 4-8-Diethylamino- α -methylbutylamino-6-*p*-chlorophenylthio-2-methylpyrimidine, 789.
 $C_{20}H_{21}O_2N_2S_2$ 4-Methyl-2-(ω -sulphanilamidodecyl)thiazole, 1377.

20 V

- $C_{20}H_{23}O_2N_2IS$ 3:4-Dimethyl-5-carbethoxymethyl-2-thiazolanyl-4-quinolylmethane methiodide, 1403.
 $C_{20}H_{21}O_2N_2Cl_2S_2$ [Bis-2-(3-ethyl- Δ^2 -thiazoline)][$\alpha\beta'$ -dimethin-2'-(3'-ethyl- Δ^2 -thiazoline)]trimethinecyanine diperchlorate, 1442.

 C_{21} Group.

- $C_{21}H_{18}$ 1:1:2-Triphenylpropylene, 437.

21 II

- $C_{21}H_{11}N_3$ 3-Cyano-9-*p*-cyanophenylphenanthridine, 86.
 7-Cyano-9-*p*-cyanophenylphenanthridine, 86.
 $C_{21}H_{11}N_2$ 6-Methyl-1:2:3:4-dibenzphenazine, 440.
 $C_{21}H_{10}O_2$ 10-Acetoxy-6-methyl-1:2-benzanthracene, 765.
 $C_{21}H_{10}O$ 1-*p*-Toluoylnaphthalene-2-carboxylic acid acetoxy-lactone, 765.
 $C_{21}H_{10}O_2$ 2-(2'-Methoxybenzoyl)-1-naphthoic acetoxy-lactone, 943.
 Methyl 1':5-dimethoxy-3:4-benzfluorenone-1-carboxylate, 226.
 $C_{21}H_{17}N_3$ 7-Anilino-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 $C_{21}H_{17}N_3$ 3-Amidino-9-*p*-amidinophenylphenanthridine, dihydrochloride, 87.
 $C_{21}H_{10}O$ 2'-Methoxy-9:10-dimethyl-1:2-benzanthracene, 942.
 $C_{21}H_{10}O_2$ 2'-Methoxy-9:10-dimethyl-1:2-benzanthracene oxide, 942.
 2':9:10-Trimethoxy-1:2-benzanthracene, 942.
 $C_{21}H_{10}N_2$ 2:6-Di-*p*-aminostyrylpyridine, 561.
 $C_{21}H_{20}O$ (+)-*dl*-1:1:2-Triphenylpropan-1-ol, 437.
 $C_{21}H_{20}O_2$ 2'-Methoxy-9:10-dihydroxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene, 942.
 $C_{21}H_{20}O_2$ 1-(*o*-Tolyl)-1:4-dihydronaphthaquinol diacetate, 1094.
 $C_{21}H_{20}O_2$ Javanicin leucoanhydrotriacetate, 1027.
 $C_{21}H_{19}As$ Phenyl-*p*-tolyl-*p*-ethylphenylarsine, and its hydroxy-picrate, 509.
 $C_{21}H_{20}N_4$ 2-(4-Diethylamino-1-methylbutylamino)-*p*-phenanthroline, tris-3:5-dinitrobenzoate, 1661.

21 III

- $C_{21}H_{14}O_2N_2$ 2-Cyano-5-phenoxy-7-methoxyacridine, 639.
 $C_{21}H_{14}O_2N_2$ 3-Nitro-6-methoxy-1:2:7:8-dibenzocarbazole, 78.
 $C_{21}H_{14}O_2N_4$ 3:4:5:6-Dibenzcyclohepta-1:3:5-trien-7-one 2:4-dinitrophenylhydrazone, 749.
 $C_{21}H_{14}NCl$ $\alpha\beta$ -Diphenyl- β -*p*-chlorophenylacrylonitrile, 642.
 $C_{21}H_{14}ON$ 9-Hydroxy-10-anthraldehyde anil, 978.
 $C_{21}H_{14}ON$ 2-Phenylcarbazolo(1':2':5:6)pyrylium hydroxide, salts, 349.
 $C_{21}H_{14}ON_2$ 7-Acetamido-9-*p*-nitrophenylphenanthridine, 72.
 4-Nitro-1'- and -4'-methoxy-1:2'- and 1:1'-azonaphthalenes, 78.
 $C_{21}H_{14}NS$ 4:6-Trimethylene-10:11-benzthionaphthindole, 657.
 4:6-Trimethylene-11:12-benzthionaphthindole, and its dipicrate, 657.
 $C_{21}H_{14}ON$ 3-Amino-6-methoxy-1:2:7:8-dibenzocarbazole, hydrochloride, 78.
 2-Phenoxy-4-phenyl-2-methyl-1:8-naphthyridine, 1410.
 4-Phenyl-3-benzylcinnoline *N*-oxide, 1651.
 $C_{21}H_{14}ON$ 3-Phenyl-4-*p*-anisylcinnoline *N*-oxide, 1651.
 $C_{21}H_{14}ON_2$ 3:4:5:6-Dibenzcyclohepta-3:5-dien-2-one 2:4-dinitrophenylhydrazone, 749.
 $C_{21}H_{17}ON$ 2-Phenyl-3-*p*-methoxyphenylindole, 1044.
 $C_{21}H_{17}ON$ *O*-Benzoylvaniillinanil, 616.
 $C_{21}H_{17}ON_2$ 2-Amidoximino-5-phenoxy-7-methoxyacridine, 639.
 Triacetyl-7-aminoquinoline, 610.
 Triacetyl-11-aminoquinoline, 610.
 $C_{21}H_{17}ON$ *O*-Benzoylvaniill- N^1 -phenylamide, 617.
 $C_{21}H_{17}ON_2$ Javanicin mono-2:4-dinitrophenylhydrazone, 1028.
 $C_{21}H_{17}ON_2$ Styrylmethylcarbonyl- α -naphthylurethane, 1096.
 $C_{21}H_{17}BrP$ 2-Phenyl-2-*p*-bromophenyl-1:2:3:4-tetrahydroisophosphinolinium bromide, 1640.
 $C_{21}H_{17}ON$ Phenyl-*p*-methoxybenzyl ketone phenylhydrazone, 1044.
 $C_{21}H_{17}ON$ 1:3:3-Trimethyl-2-(3'-benzoylallylidene)dihydroindole, 1630.
 $C_{21}H_{17}OP$ 2-Phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophosphinolinium hydroxide, salts of, 1641.
 $C_{21}H_{17}OSb$ Trianisyletlibines, 1569.
 $C_{21}H_{17}ON$ 8- γ -Phthalamidopropylamino-6-methoxyquinoline, 1337.
 $C_{21}H_{17}NS$ 4-Methyl-3-ethyl-2-dianiloisopropylidene- Δ^2 -thiazoline, 1440.
 $C_{21}H_{25}ON$ *neo*Strychnine, preparation of, 78.
 $C_{21}H_{25}ON$ Oxodihydro*neo*strychnine, and its hydrobromide, 1556.
 neo Strychnine *N*-oxide, and its benzoate, 80.
 $C_{21}H_{25}ON_4$ *O*-2:4:6-Trinitrobenzoyl-*N*-hexovanillylamide, 615.
 $C_{21}H_{25}ON_2$ 2:7-Dicarbethoxyamino-9:10-dimethylphenanthridine, salts, 72.
 $C_{21}H_{25}ON_2$ *O*-Dinitrobenzoyl-*N*-hexovanillylamides, 615.
 $C_{21}H_{25}ON_2$ Dibenzoyltrimethylhexahydropyrimidine, 1398.
 1-Diethylamino-4-en-2-yn-6-yl α -naphthylurethane, 1579.
 $C_{21}H_{25}ON_2$ 3-Nitro-4:5-di-*tert.*-butylnaphtha-*N*-methylimide, 745.
 $C_{21}H_{25}ON_2$ *O*-*p*-Nitrobenzoyl-*N*-hexovanillylamide, 615.
 $C_{21}H_{25}ON_2$ *O*-5-Nitrosalicyl-*N*-hexovanillylamide, 615.
 $C_{21}H_{25}ON$ 4- β -Diethylaminoethylamino-2-phenoxyquinoline, 909.

- C₂₁H₂₁O₂N** Piperidinoethyl benzoate, 60.
C₂₁H₂₁O₂N *O*-Benzoyl-*N*-hexoanillylamide, 615.
C₂₁H₂₁O₂N Citrylideneacetaldehyde 2:4-dinitrophenylsemicarbazone, 1390.
C₂₁H₂₁N₂Cl 4-*p*-Chloroanilino-2- β -diethylaminoethylaminoquinoline, and its dihydride, 905.
C₂₁H₂₁N₂Cl 2-Amino-4-*p*-chloroanilino-6-dimethylaminopropylamino-5-phenylpyrimidine, 1363.
C₂₁H₂₁N₂Cl₂ 2:4-Di-*p*-chloroanilino-6- β -diethylaminoethylamino-1:3:5-triazine, dihydrochloride, 159.
C₂₁H₂₁O₂N₂ *NN'*-2:4-Dibenzamido-2:3-dimethylpentane, 1491.
C₂₁H₂₁O₂N₂ Methyl 1-tetra-acetyl-*d*-glucosidoglyoxaline-4:5-dicarboxylate, 380.
C₂₁H₂₁O₂N γ -Dimethylamino- $\beta\beta$ -dimethylpropyl benzoate, 60.
C₂₁H₂₁ON 4-(8'-Methoxy-6'-quinolylamino)-2- β -diethylaminoethylamino-6-methylpyrimidine, and its trihydrochloride, 1619.
C₂₁H₂₁O₂N 1:3-(*pp'*-Bisacetamidomethylidiphenoxy)propane, 1454.
C₂₁H₂₁ON 3- β -Diethylaminoethylamino-4'-methoxy-4:5-dimethyldiphenylamine, 914.
C₂₁H₂₁N₂Cl 4-*p*-Chloroanilino-6- β -diethylamino- α -methylbutylamino-2:5-dimethylpyrimidine, 1359.
C₂₁H₂₁O₂N Nonoxynonylurethane, 967.

21 IV

- C₂₁H₁₃O₂N₂S₂** 2:4:6:8-Tetranitro-1:5-di-*m*-nitrobenzenesulphonamide, 81.
C₂₁H₁₃O₂NCl Ethyl 4-chloro-2-phthalimidobenzoylacetate, 235.
C₂₁H₁₇ONS 2-Benzylmethylaminothioxanthone, 1233.
C₂₁H₁₈O₂NCl *p*-Chlorostyrylmethylcarbonyl- α -naphthylurethane, 1095.
C₂₁H₁₈O₂NBr *p*-Bromostyrylmethylcarbonyl- α -naphthylurethane, 1095.
C₂₁H₁₈O₂NF *p*-Fluorostyrylmethylcarbonyl- α -naphthylurethane, 1095.
C₂₁H₁₈ON₂Cl α -*p*-Toluidinophenylacet-*p*-chloroanilide, 1044.
C₂₁H₁₈O₂N 4-Benzylmethylamino-2'-carboxydiphenyl sulphide, 1232.
C₂₁H₁₈O₂NS₂ 4-Benzylmethylamino-2'-carboxydiphenyl sulphide 3-sulphonic acid, 1233.
C₂₁H₂₀OBrP 2-Phenyl-2-*p*-bromophenyl-1:2:3:4-tetrahydroisophospholinium hydroxide, salts of, 1641.
C₂₁H₂₀O₂N₂S₂ 2-Phenyl-2-*p*-hydroxyphenyl-1:2:3:4-tetrahydroisophospholinium bromide, 1641.
C₂₁H₂₀O₂N₂S₂ 4-Dimethylamino-2'-*N*-benzenesulphonylcarbonyldiphenyl sulphide, 1231.
C₂₁H₂₀O₂NS 4-Ethylamino-2'-*N*-benzenesulphonylcarbonyldiphenyl sulphide, 1232.
C₂₁H₂₁O₂Cl₂Sb Trianisylstibine dichlorides, 1570.
C₂₁H₂₁O₂Br₂Sb Trianisylstibine dibromides, 1570.
C₂₁H₂₁O₂I₂Sb Trianisylstibine diiodides, 1570.
C₂₁H₂₂O₂NP Dibenzyl *N*-methylanilinophosphonate, 677.
C₂₁H₂₂O₂NS₂ Dibenzyl *p*-toluidinophosphonate, 677.
C₂₁H₂₇O₂NS₂ 3-Nitro-1:5-di-*p*-tolylsulphonyl-3-ethylpentane, 1516.
C₂₁H₃₀ON₂S 4-Methyl-2-(ω -benzamido)decylthiazole, 1377.
C₂₁H₃₂ON₂S 2- β -Diethylamino- α -methylbutylamino-4-*p*-methoxyphenylthio-6-methylpyrimidine, 788.

21 V

- C₂₁H₁₉N₂Cl₂IS₂** Bis-2-(5-chloro-3-ethylbenzthiazole)trimethinecyanine iodide, 957.

C₂₂ Group.

- C₂₂H₁₄** 1:2:5:6-Dibenzanthracene, crystal structure of, 1001.

22 II

- C₂₂H₁₅N₃** 7-Benzylideneaminoquinoline, 610.
C₂₂H₁₇N₃ $\beta\beta$ -Diphenyl- α -*p*-tolylacrylonitrile, 642.
C₂₂H₁₈O₂ $\beta\beta$ -Diphenyl- α -*p*-tolylacrylic acid, 642.
C₂₂H₂₀O₂ Dimethyl 2':5'-dimethoxy-1-phenylnaphthalene-2:3-dicarboxylate, 226.
C₂₂H₂₄O₄ 6:7-Dimethoxy-1-veratryl-2-methyl-1:2-dihydronaphthalene-3-carboxylic acid, 951.
C₂₂H₂₆O₄ 5:6-Dimethoxy-3-veratryl-2-methyl-1-ethylindene, 951.
C₂₂H₂₆O₄ 6:7-Dimethoxy-1-veratryl-2-methyl-1:2:3:4-tetrahydronaphthalene-3-carboxylic acid, 951.
C₂₂H₂₆O₄ 5:6-Dimethoxy-3-veratryl-2-methyl-1-ethylhydrindene, 951.
C₂₂H₂₆O₄ 2:3:6:7-Tetramethoxy-9:10-diethyl-9:10-dihydroanthracene, 950.
C₂₂H₂₆S₂ Dihydromycene bis(phenyl sulphide), 40.
C₂₂H₂₈N₂ 2:4-Bis-(γ -diethylaminopropylamino)quinazoline, and its tripicrate, 777.

22 III

- C₂₂H₁₇ON** 7-Cyano-9-*p*-cyanophenyl-10-methylphenanthridinium hydroxide, salts, 87.
C₂₂H₁₇O₂N₂ 7-Acetamido-9-*o*-nitrophenylphenanthridine, 73.
C₂₂H₁₇ONCl β -Phenyl- β -*p*-chlorophenyl- α -*p*-tolylacrylonitrile, 643.
C₂₂H₁₇ON *cis*- and *trans*- $\alpha\beta$ -Diphenyl- β -*p*-anisylacrylonitriles, 643.
C₂₂H₁₇ON 2-Methoxy-1-naphthylmethylene- α -naphthylamine, 1047.
C₂₂H₁₇ON 3-(α - and β -Naphthylamino)-4:5-benzocoumarans, 1047.
C₂₂H₁₇O₂N 5-Phenylpent-2-en-4-yn-tyl α -naphthylurethane, 1585.
C₂₂H₁₇O₂N 3-*O*-4'-Benzoyloxy-3'-methoxyphenylindole, 1695.
C₂₂H₁₇O₂N 7-Carbethoxyamino-9-*o*-nitrophenylphenanthridine, 73.
C₂₂H₁₇O₂N 7-Carbethoxyamino-9-*p*-nitrophenylphenanthridine, 72.
C₂₂H₁₇O₂N 8-Nitro-1:5-dimethoxynaphthaleneazo- β -naphthol, 354.
C₂₂H₁₇O₂N 2-(2':4'-Dinitrophenylamino)isindolinone-3-acetanilide, 832.
C₂₂H₁₇O₂N 1-Hydroxy-3-(2':4'-dinitrophenyl)-3:4-dihydrophthalazine-4-acetanilide, 833.
C₂₂H₁₇N₂Cl 2:4-Di-*p*-chloroanilino-3-methylquinoline, 908.
C₂₂H₁₇O₂N $\alpha\beta$ -Bis-6-methoxyquinolyl(4)ethylene, 1686.
C₂₂H₁₇O₂N 1:5-Dimethoxynaphthaleneazo- β -naphthol, 354.
C₂₂H₁₇O₂N 7-Acetamido-9-*o*-nitrophenyl-10-methylphenanthridine, methosulphate, 73.

- $C_{15}H_{13}ON$ $\alpha\beta$ -Diphenyl- β -*p*-tolylacrylamide, 642.
 $\beta\beta$ -Diphenyl- α -*p*-tolylacrylamide, 642.
 $C_{15}H_{13}ON$ 2-Phenyl-3-*p*-methoxyphenyl-5-methylindole, 1044.
 $C_{15}H_{13}ON$ *cis*- and *trans*- $\alpha\beta$ -Diphenyl- β -*p*-anisylacrylamides, 643.
 $C_{15}H_{13}OSb$ 10-*p*-Carbethoxyphenyl-2-methylphenoxstibine, 8.
 $C_{15}H_{13}ON$ Phenyl α -(*o*-carboxyanilino)-*p*-methoxybenzyl ketone, 1044.
 $C_{15}H_{13}ON$ 2-*o*-Nitrobenzamido-4'-carbethoxyaminodiphenyl, 73.
 $C_{15}H_{13}ON$ 2-*p*-Nitrobenzamido-4'-carbethoxyaminodiphenyl, 72.
 $C_{15}H_{13}ONCl$ 7-Amidino-9-*p*-amidinophenyl-10-methylphenanthridinium chloride, and its dihydrochloride, 87.
 $C_{15}H_{13}ON$ Methylstyrylmethylcarbinylnaphthylurethanes, 1094.
 $C_{15}H_{13}ON$ *p*-Methoxystyrylmethylcarbinylnaphthylurethane, 1096.
 $C_{15}H_{13}ONCl_2$ Bis-2-(5-*p*-tolylpyrrole)azamethin dihydrochloride, 1200.
 $C_{15}H_{13}ON$ 1:3:3-Trimethyl-2-(3'-*m*-methoxybenzoylallylidene)dihydroindole, 1630.
 $C_{15}H_{13}ONCl_3$ 1:1:1-Trichloro-2:2-di-(4-*o*-carbethoxymethoxyphenyl)ethane, 849.
 $C_{15}H_{13}ON_3$ 3-Nitro-4-piperidino-1:2-diphenyl-*n*-butyleyanide, 1508.
 $C_{15}H_{13}ON_3$ 1:1-Di(benzamidomethyl)cyclohexane, 1519.
 $C_{15}H_{13}ON$ Dibenzoyl derivative of α -ethyl- α -*n*-butylacetamide, 741.
 $C_{15}H_{13}ON_2$ $\beta\beta$ -*N*-(*b*)-Hydroxymethylidihydroxystrychnine, 1559.
 $C_{15}H_{13}ONCl_2$ 7-Chloro-2-*p*-chloroanilino-4- γ -diethylaminopropylaminoquinoline, 908.
 $C_{15}H_{13}ON$ 2-Dimethylaminocyclohexyl benzilate, and its salts, 167.
 $C_{15}H_{13}ONCl$ 2-*p*-Chloroanilino-4- γ -diethylaminopropylaminoquinoline, and its dihydrochloride, 905.
 $C_{15}H_{13}ONCl$ 2-Amino-4-*p*-chloroanilino-6-diethylaminoethylamino-5-phenylpyrimidine, 1363.
 $C_{15}H_{13}ON$ 2-*p*-Chlorophenylguanidino-4- β -diethylaminoethylaminoquinoline, 909.
 $C_{15}H_{13}ON$ 2-Acetamido-3:4-di-*tert*-butylacenaphthene, 744.
 $C_{15}H_{13}ON$ 4-Diethylamino-2-butyl benzilate, and its salts, 166.
 $C_{15}H_{13}ON$ 2-Keto-1- β -diethylamino-1- β -carbethoxyisopropyl-1:2:3:4-tetrahydronaphthalene, 400.

22 IV

- $C_{22}H_{15}O_2N_2S_2$ 2:4:6:8-Tetranitro-1:5-di-*m*-nitrobenzenesulphonamidonaphthalene, 81.
 $C_{22}H_{15}ONCl$ β -Phenyl- β -*p*-chlorophenyl- α -*p*-tolylacrylamide, 643.
 $C_{22}H_{15}ONCl$ 3-Phenyl-4-*p*-hydroxyphenylcinnoline ethiodide, 1654.
 $C_{22}H_{15}ONAs$ 2-Hydroxynaphthalene-1-azo-*p*-phenylbis-2-cyanoethylarsine, 621.
 $C_{22}H_{15}ONCl$ 7-Acetamido-9-*o*-aminophenyl-10-methylphenanthridinium chloride, 73.
 $C_{22}H_{15}ON_2Cl_2$ Bis-2-(5-methoxyphenylpyrrole)azamethin dihydrochlorides, 1200.
 $C_{22}H_{15}ON_2S_2$ 4:6-Bis-*p*-acetamidophenylsulphonyl-2-methylpyridine, 55.
 $C_{22}H_{15}ON_2S_2$ Phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine, 1640.
 $C_{22}H_{15}ON_2S_2$ 4-Methylethylamino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide, 1232.
 $C_{22}H_{15}ONCl$ 2-Dimethylaminocyclohexyldiphenylchloroacetate, hydrochloride, 167.
 $C_{22}H_{15}ONClS$ 2-*p*-Chlorophenylthioureido-4- β -diethylaminoethylaminoquinoline, 909.
 $C_{22}H_{15}ONCl$ 4-Diethylamino-2-butyl diphenylchloroacetate, hydrochloride, 166.
 $C_{22}H_{15}ONClS$ 2- γ -Di-*n*-butylaminopropylamino-4-*p*-chlorophenylthio-6-methylpyrimidine, and its dipicrate, 788.
 $C_{22}H_{15}ON_2S_2$ 4-Methyl-2-(ω -acetylsulphanilamidodecyl)thiazole, 1377.
 $C_{22}H_{15}ON_2S_2$ *N*-(*p*-Aminobenzenesulphonyl)- α -ethyl- α -*n*-butyl-*sec*-octylacetamide, 742.

 C_{23} Group.

- $C_{23}H_{14}S$ 9- α -Naphthylthioxanthen, 999.
 $C_{23}H_{14}O$ 9:10-Dihydroxyphenanthrene 2:4-dimethoxyphenylhydroxymethylene ether, 1000.
 $C_{23}H_{14}O$ ω -Methoxy-2:4-dibenzoylresacetophenone, 1683.
 $C_{23}H_{14}O$ 2':9:10-Trimethoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene, 942.
 $C_{23}H_{14}O$ Ethyl α -(2-methoxy-3:5-dimethylbenzoyl)butane- $\beta\gamma$ -tricarboxylate, 538.

23 III

- $C_{23}H_{14}OS$ 9- α -Naphthylthioxanthhydrol, 999.
 $C_{23}H_{14}ON$ 4'-Nitro-1:2'-dimethoxy-3-phenyl-4-(2'':4''-dinitrobenzylidene)-3:4-dihydrophthalazine, 467.
 $C_{23}H_{14}ON$ *cis*- and *trans*- $\alpha\beta$ -Diphenyl- β -3:4-dimethoxyphenylacrylonitriles, 643.
 $C_{23}H_{14}ON$ β -Phenyl- $\alpha\beta$ -di-*p*-anisylacrylonitrile, 643.
 $C_{23}H_{14}ON$ 7-Carbethoxyamino-9-*p*-nitrophenyl-10-methylphenanthridine, salts, 72.
 $C_{23}H_{14}ONCl_2$ 2:4-Di-*p*-chloroanilino-3-ethylquinoline, 909.
 $C_{23}H_{14}ON_3$ 7-Carbethoxyamino-9-*o*-nitrophenyl-10-methylphenanthridine, methosulphate, 73.
 $C_{23}H_{14}ON_2S_2$ 2:4-Dithio-5-phenyl-1:3-dibenzylhydantoin, and its hydrochloride, 1607.
 $C_{23}H_{14}ON$ $\alpha\beta$ -Diphenyl- β -3:4-dimethoxyphenylacrylamide, 643.
 $C_{23}H_{14}ON$ *trans*- β -Phenyl- $\alpha\beta$ -di-*p*-anisylacrylamide, 643.
 $C_{23}H_{14}ONCl$ 2:8-Dichloro-5-(γ -butylaminopropylamino)-3:4:2':3'-pyridoacridine, 680.
 $C_{23}H_{14}ONCl$ 2:8-Dichloro-5-(γ -diethylaminopropylamino)-3:4:2':3'-pyridoacridine, 680.
 $C_{23}H_{14}OP$ Phenyl-*p*-anisyl-2-(*o*-methoxymethylphenyl)ethylphosphine, 1641.
 $C_{23}H_{14}ONCl$ 2-Chloro-5-(γ -diethylaminopropylamino)-3:4:2':3'-pyridoacridine, 680.
 $C_{23}H_{14}ON_2$ *neo*Brucine, preparation of, and its methosulphate, 80.
 $C_{23}H_{14}ON_2$ *neo*Brucine *N*-oxide, 80.
 $C_{23}H_{14}ON$ Oxodihydromethoxymethylidihydroxystrychnine, 1555.
 $C_{23}H_{14}ONCl$ 4-*p*-Chloroanilino-6- β -diethylaminoethylamino-5-phenyl-2-methylpyrimidine, 1361.
 $C_{23}H_{14}ON$ α - and β -4-Benzilyloxy-1:2:2:6-tetramethylpiperidines, 60.
 $C_{23}H_{14}ONCl$ 2-*p*-Chloroanilino-4- γ -diethylaminopropylamino-3-methylquinoline, perchlorate, 908.
 $C_{23}H_{14}ONCl$ 2-Amino-4-*p*-chloroanilino-6-diethylaminopropylamino-5-phenylpyrimidine, 1363.
 $C_{23}H_{14}ON$ 2-*p*-Chlorophenylguanidino-4- γ -diethylaminopropylaminoquinoline, 909.
 $C_{23}H_{14}ON$ Dibenzylaminoisopropylamino-2-methylpentane, 1398.
 $C_{23}H_{14}ON_2$ 1:5-(*pp'*-Bisacetamidomethyldiphenoxy)pentane, 1454.

$C_{23}H_{24}N_2Cl$ 4'-Chloro-3-(δ -diethylamino- α -methyl-*n*-butylamino)-4:5-dimethyldiphenylamine, 913.
 $C_{23}H_{26}O_2N_2$ *NN'*-Di-(2-ethoxyethyl)ethylenediamine-*N*-carboxy(ethyl-2-ethoxyethyl)amide-*N'*-carboxy-piperidine, 318.

23 IV

$C_{23}H_{21}O_2N_2Cl$ Bis-3-(2-methoxy-5-phenylpyrrole)methin hydrochloride, 1195.
 $C_{23}H_{21}O_2N_2Cl$ 2-*p*-Chloroanilino-4:6-di-*p*-anisidino-1:3:5-triazine, hydrochloride, 160.
 $C_{23}H_{21}O_2N_2S_2$ 6-Nitro-2- β -anilino-*vinyl*benzthiazole metho-*p*-toluenesulphonate, 957.
 $C_{23}H_{21}O_2N_2S$ 7-Acetamido-9-*p*-nitrophenyl-10-methylphenanthridinium methosulphate, 72.
 $C_{23}H_{21}O_2N_2As$ Diphenylmethyl-2-cyano-*n*-propylarsonium picrate, 622.
 $C_{23}H_{21}N_2ClIS$ Bis-2-(5-chloro-3-ethylbenzthiazole)pentamethincyanine iodide, 1443.
 $C_{23}H_{23}O_2N_2Cl$ 7-Carbethoxyamino-9-*o*-aminophenyl-10-methylphenanthridinium chloride, 73.
 $C_{23}H_{23}O_2N_2BrP$ 7-Carbethoxyamino-9-*p*-aminophenyl-10-methylphenanthridinium chloride, 73.
 $C_{23}H_{23}O_2N_2S$ 2-Phenyl-2-*p*-acetoxyphenyl-1:2:3:4-tetrahydroisophosphinolinium bromide, 1641.
 $C_{23}H_{23}O_2N_2S$ 2-Phenyl-2-*p*-aminophenyl-10-methylphenanthridinium methosulphate, 73.
 $C_{23}H_{23}O_2N_2S$ *N*⁴-Acetylsulphanilyl-*O*-acetylvanill-*N*¹-phenylamidine, 617.
 $C_{23}H_{23}O_2N_2I$ 7-Carbethoxy-4-*p*-dimethylaminostyryl-1-ethylcinnolinium iodide, 811.
 $C_{23}H_{23}ON_2S$ 2-*p*-Chlorophenylthioureido-4- γ -diethylaminopropylaminoquinoline, 909.
 $C_{23}H_{26}ON_2S$ 2- γ -Di-*n*-butylaminopropylamino-4-*p*-methoxyphenylthio-6-methylpyrimidine, and its dipicrate, 788.

23 V

$C_{23}H_{21}OBrIP$ Phenyl-*p*-bromophenyl-2-(*o*-methoxymethylphenyl)ethylphosphine methiodide, 1640.

 C_{24} Group.

$C_{24}H_{18}O_4$ Deca-2:8-dien-4:6-diyne-1:10-diyl dibenzoate, 1589.
 $C_{24}H_{20}O_2$ 9:10-Dihydroxyphenanthrene cuminyldihydroxymethylene ether, 1000.
 $C_{24}H_{22}O_2$ 6-Methoxy-2:3-di-*p*-methoxyphenylindene, 1697.
 $C_{24}H_{27}N_3$ Tris(benzylmethyleneimine), methiodide, 1118.
 $C_{24}H_{28}O_6$ Diacetyl guaiaretic acid, 950.
 $C_{24}H_{30}O_6$ Diacetyl dihydroguaiaretic acid, 950.
 $C_{24}H_{40}O_4$ 3(β):6(β)-Dihydroxycholan-ic acid, 814.

24 III

$C_{24}H_{17}N_2S_2$ Azamethin[2-(4-phenylthiazole)][2-(3:4-diphenyl-2:3-dihydrothiazole)], and its dihydrobromide, 1658.
 $C_{24}H_{19}O_2N_4$ 3:3'-Dinitro-4:4'-diacetamido-1:1'-dinaphthyl, 1573.
 $C_{24}H_{19}O_2N_4$ 4:4'-Dinitro-1:1'-diacetamido-1:1'-dinaphthyl, 1574.
 $C_{24}H_{19}O_2N_4$ Deca-4:6-diyne-2:9-diol bis-3:5-dinitrobenzoate, 1582.
 $C_{24}H_{19}ClAs$ Phenyl-*p*-phenyl-*p*-chlorophenylarsine, 510.
 $C_{24}H_{19}ON$ 4-(3':5'-Dibenzoylpenta-2':4'-dienylidene)-1:4-dihydropyridine, 1629.
 $C_{24}H_{21}ON_3$ 3-Ethyl-2-dianiloisopropylidenebenzoxazoline, 1441.
 $C_{24}H_{21}ON$ α -*p*-Tolyl- $\beta\beta$ -di-*p*-anisylacrylonitrile, 643.
 $C_{24}H_{21}ON$ 3-(α -Naphthylacetamido)-4:5-benzocoumaran, 1047.
 $C_{24}H_{21}N_2Se$ 3-Ethyl-2-dianiloisopropylidenebenzselenazoline, 1439.
 $C_{24}H_{23}O_2N_4$ 3:3'-Diamino-4:4'-diacetamido-1:1'-dinaphthyl, and its dihydrochloride, 1574.
 $C_{24}H_{23}O_2N_4$ α -*p*-Tolyl- $\beta\beta$ -di-*p*-anisylacrylamide, 643.
 $C_{24}H_{26}O_2N_4$ 8- γ -Phthalimidopropyl- γ -aminopropylamino-6-methoxyquinoline, hydrobromide, 1336.
 $C_{24}H_{27}OSb$ Tri-*o*-phenetylstibine, 1569.
 $C_{24}H_{27}N_2Cl$ 8-Chloro-2-methyl-5-(γ -diethylaminopropylamino)-3:4:2':3'-pyrrodoacridine, 681.
 $C_{24}H_{30}N_2Cl$ 4-*p*-Chloroanilino-6- γ -diethylaminopropylamino-5-phenyl-2-methylpyrimidine, 1361.
 $C_{24}H_{31}ON$ 4-Benzyl-1:2:2:6:6-pentamethylpiperidine, 60.
 $C_{24}H_{31}ON$ 2-Diethylaminocyclohexyl benzilate, and its salts, 167.
 $C_{24}H_{37}ON_2$ 3- δ -Diethylamino- α -methyl-*n*-butylamino-4'-methoxy-4:5-dimethyldiphenylamine, 914.
 $C_{24}H_{37}ON$ Phthalocetyl-1,9-dione, 199.
 $C_{24}H_{37}ON_2$ 3(β):6(β)-Diacetoxystiecholan-17-one semicarbazone, 814.

24 IV

$C_{24}H_{17}ONCl_2$ 4-(3':5'-Di-*o*-chlorobenzoylpenta-2':4'-dienylidene)-1:4-dihydropyridine, 1629.
 $C_{24}H_{19}OClAs$ Phenyl-*p*-phenyl-*p*-chlorophenylarsine oxide, 510.
 $C_{24}H_{19}O_2N_2S_2$ 2:4:5:7-Tetranitro-1:8-di-*p*-toluenesulphonamidonaphthalene, 81.
 $C_{24}H_{19}O_2N_2S_2$ 2:4:6:8-Tetranitro-1:5-di-*p*-toluenesulphonamidonaphthalene, 81.
 $C_{24}H_{20}ON_2S_2$ Bistoluene-*p*-sulphonyl-6-nitro-2-naphthylamine, 330.
 $C_{24}H_{20}ON_2S_2$ Bistoluene-*p*-sulphonyl-7-nitro-2-naphthylamine, 330.
 $C_{24}H_{20}ON_2S$ 5-Chloro-3-ethyl-2-dianiloisopropylidenebenzthiazoline, 1439.
 $C_{24}H_{21}ON_2S_2$ 2:4:6-Tris-*p*-methylsulphonylphenyl-1:3:5-triazine, 1113.
 $C_{24}H_{23}ON_2Cl$ 7-Acetamido-9-*o*-acetamidophenyl-10-methylphenanthridinium chloride, 74.
 $C_{24}H_{23}ONP$ Dibenzyl β -naphthylaminophosphonate, 677.
 $C_{24}H_{24}ON_2I_2$ 3-Phenyl-4-*p*-hydroxyphenylcinnoline diethiodide, 1655.
 $C_{24}H_{25}ON_2Cl_2$ Bis-2-(5:3:4-dimethoxyphenylpyrrole)azamethin dihydrochloride, 1200.
 $C_{24}H_{27}OCl_2Sb$ Tri-*o*-phenetylstibine dichloride, 1570.
 $C_{24}H_{27}OBr_2Sb$ Tri-*o*-phenetylstibine dibromide, 1570.
 $C_{24}H_{27}OI_2Sb$ Tri-*o*-phenetylstibine diiodide, 1570.
 $C_{24}H_{28}OIP$ Phenyl-*p*-anisyl-2-(*o*-methoxymethylphenyl)ethylphosphine methiodide, 1641.
 $C_{24}H_{28}ONCl$ 2-Diethylaminocyclohexyl diphenylchloroacetate, hydrochloride, 167.
 $C_{24}H_{41}ON_2S$ *N*-(*p*-Acetamidobenzenesulphonyl)- α -ethyl- α -*n*-butyl- α -sec.-octylacetamidine, 742.

24 V

- $C_{11}H_{12}OCIBrP$ 2-*p*-Tolyl-2-*p*-chlorophenacyl-1:2:3:4-tetrahydroisophospholinium bromide, 1639.
 $C_{11}H_{12}N_2Cl_2As_2Pd$ Dichlorodi-(*p*-chlorophenylbis-2-cyanoethylarsine)palladium, 621.
 $C_{11}H_{12}N_2Cl_2As_2Pd$ Dichlorodi(phenylbis-2-cyanoethylarsine)palladium, 621.

C₂₅ Group.

- $C_{25}H_{19}N_3$ 2:8-Bis(phenylamino)acridine, hydrochloride, 247.
 $C_{25}H_{21}N_3$ α -Phenyl- $\beta\beta'$ -bis-(*p*-dimethylaminophenyl)acrylonitrile, 643.
 $C_{25}H_{43}O_4$ α -Monobrassicidin, 558.
 α -Monoerucin, 558.

25 III

- $C_{25}H_{19}O_2N_2$ 2-Benzidino-2-hydroxyperinaphthindan-1:3-dione, 130.
 $C_{25}H_{19}ON$ 3:5-Diphenyl-2-(2'-benzoylviny)pyrrole, 1631.
 $C_{25}H_{21}O_2N$ 4-(3':5'-Dibenzoyl-1'-methylpenta-2':4'-dienylidene)-1:4-dihydropyridine, 1629.
 $C_{25}H_{23}O_2N_2$ 2:4:6-Tribenzoyloxypyrimidine, 730.
 $C_{25}H_{25}IAs$ Triphenyl-*m*-tolylarsonium iodide, 508.
 $C_{25}H_{23}O_2N_2$ 2-Hydroxy-2-phenyl-2:3-dihydroroteneoxazole, 653.
 $C_{25}H_{23}O_2N_2$ 2:7-Dicarbethoxyamino-9-phenylphenanthridine, and its mesosulphate, 71.
 $C_{25}H_{23}O_2N$ Phenyl *N*-methylmesidino-*p*-methoxybenzyl ketone, 1044.
 $C_{25}H_{27}O_2N$ γ -Dimethylaminoethyl- α -phenylpropyl benzilate, and its methochloride, 168.
 $C_{25}H_{23}O_2N_4$ 4- γ -Diethylaminopropylamino-2:6-dibenzoyloxypyrimidine, and its dipicrate, 731.
 $C_{25}H_{43}O_2N$ Ricinoleovanillylamide, 614.

25 IV

- $C_{25}H_{21}ON_2Cl_2$ β -*p*-Chlorobenzoylpropionitrile phenylhydrazone, 1193.
 $C_{25}H_{21}O_2N_2Cl$ 7-Acetamido-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium chloride, 73.
 7-Carbethoxyamino-9-*o*-acetamidophenyl-10-methylphenanthridinium chloride, 73.
 7-Carbethoxyamino-9-*p*-acetamidophenyl-10-methylphenanthridinium chloride, 73.
 $C_{25}H_{21}O_2N_2Cl$ Bis-3-(2-ethoxy-5-phenylpyrrole)methin hydrochloride, 1195.

25 V

- $C_{25}H_{26}ClIBrIAs$ Phenyl-*p*-tolyl-*p*-chlorophenyl-*p*-bromophenylarsonium iodide, 511.
 $C_{25}H_{21}OCIBrAs$ Phenyl-*p*-tolyl-*p*-chlorophenyl-*p*-bromoarsonium hydroxide, salts, 511.

C₂₆ Group.

- $C_{26}H_{18}O_4$ 9:10-Dihydroxyphenanthrene 2-methoxy-1-naphthylhydroxymethylene ether, 1000.
 $C_{26}H_{24}N_2$ 1-Ethyl-2- and -4-daniloisopropylidene-1:2- and -1:4-dihydroquinolines, 1440.
 $C_{26}H_{40}O_2$ 10:15-Dimethyltetracos-11:13-diyne-10:15-diol, 1583.

26 III

- $C_{26}H_{22}O_2N$ 4-(3':5'-Di-*m*-methoxybenzoylpenta-2':4'-dienylidene)-1:4-dihydropyridine, 1629.
 $C_{26}H_{24}IAs$ Triphenyl-*p*-ethylphenylarsonium iodide, 508.
 $C_{26}H_{24}O_2N$ 2-Hydroxy-2-anisyl-2:3-dihydroroteneoxazole, 653.
 $C_{26}H_{24}O_2N_2$ 2'(or 5')-Nitro-9'-keto-3'-4'-di-*tert*.-butyl-8'-azaphenalino(7':8':2:3)- ψ -indole, 745.
 $C_{26}H_{24}O_2N$ 3-Nitro-4:5-di-*tert*.-butylnaphthalic 2:4-dinitrophenylhydrazide, 745.
 $C_{26}H_{26}N_2Cl$ 2-*p*-Chloroanilino-4- γ -diethylaminopropylamino-7:8-benzoquinoline, and its dihydrochloride, 906.
 $C_{26}H_{26}O_2N$ 4- γ -Diethylaminopropylamino-2:6-dibenzoyloxy-5-methylpyrimidine, and its tripicrate, 731.
 $C_{26}H_{26}N_2Cl$ 4-*p*-Chloroanilino-2- γ -di-*n*-butylaminopropylaminoquinoline, and its dihydride, 90.
 $C_{26}H_{30}O_2N$ 1:12-Dodecamethylenedi-*O*-benzamidoxime, 968.
 $C_{26}H_{41}O_2N$ Chaulmoogrovanillylamide, 615.
 $C_{26}H_{41}O_2N$ Oleovanillylamide, 614.

26 IV

- $C_{26}H_{19}ON_2Cl_2$ 3:7:3':7'-Tetrachloro-2:8:2':8'-tetra-amino-5:10-dihydrodiacridyl 5:5'-ether, 249.
 $C_{26}H_{19}O_2N_2S_2$ Dithiobenzo-*p*-nitroanilide, 1234.
 $C_{26}H_{21}ClIAs$ Phenyl-*p*-tolyl-*m*-tolyl-*p*-chlorophenylarsonium iodide, 509.
 $C_{26}H_{21}ON_2Br$ Phenyl-*p*-tolyl-*m*-tolyl-*p*-chlorophenylarsonium iodide, 509.
 $C_{26}H_{21}N_2IS_2$ 2'(or 5')-Bromo-9'-keto-3'-4'-di-*tert*.-butyl-8'-azaphenalino(7':8':2:3)- ψ -indole, 746.
 $C_{26}H_{27}N_2IS_2$ Bis-2-(3-ethylbenzthiazole)methylheptamethincyanine iodides, 962.
 $C_{26}H_{27}N_2IS_2$ Bis-2-(3-ethylbenzselenazole)- γ -methylheptamethincyanine iodide, 962.

26 V

- $C_{26}H_{26}ClIBrIAs$ Phenyl-4-*o*-xylyl-*p*-chlorophenyl-*p*-bromophenylarsonium iodide, 512.
 $C_{26}H_{26}OCIBrAs$ Phenyl-4-*o*-xylyl-*p*-chlorophenyl-*p*-bromophenylarsonium hydroxide, salts, 512.

C₂₇ Group.

- $C_{27}H_{31}N$ Tri-*n*-nonylamine, and its oxalate, 200.

27 IV

- $C_{27}H_{21}O_2N_2S_2$ 4-Benzylmethylamino-2'-*N*-benzenesulphonylcarbamyldiphenyl sulphide, 1232.
 $C_{27}H_{21}ClIAs$ *m*-Tolyl-di-*p*-tolyl-*p*-chlorophenylarsonium iodide, 513.
 $C_{27}H_{21}O_2N_2Cl$ Bis-3-(2-ethoxy-5-phenylpyrrole)trimethin hydrochloride, 1195.

- $C_{17}H_{23}O_2N_2Cl$ Bis-3-(2-ethoxy-5-4'-methoxyphenylpyrrole)methin hydrochloride, 1195.
 $C_{17}H_{23}N_2IS_2$ Bis-2-(3-ethylbenzthiazole)dimethylheptamethincyanine iodides, 962.
 $C_{17}H_{23}N_2ISe_2$ Bis-2-(3-ethylbenzselenazole)- $\beta\beta'$ -dimethylheptamethincyanine iodide, 962.
 $C_{17}H_{23}O_2N_2P$ 2'-3'-*iso*Propylidene adenosine-5'-dibenzyl phosphate, 650.
 $C_{27}H_{34}O_2AsI$ Phenylmethylbis-3-benzylxypropylarsonium iodide, 624.

C₂₈ Group.

- $C_{28}H_{18}O_3$ Substance, from phenanthraquinone and diphenylketen, 999.
 $C_{28}H_{18}O_7$ *p*-Benzoyloxybenzoic anhydride, 123.
 $C_{28}H_{20}O_2$ Diphenylketen, dimer, 175.

28 III

- $C_{28}H_{11}N_2Cl_2$ Bis-2-(5-*p*-chlorophenylpyrrole)azamethin dihydrochloride, 1200.
 $C_{28}H_{11}N_2Cl_2$ Bis-2-(5-naphthylpyrrole)azamethin dihydrochlorides, 1200.
 $C_{28}H_{23}N_2S$ 3-Ethyl-2-dianilo*iso*propylidene-6:7-benzbenzthiazoline, 1439.
 $C_{28}H_{24}ON_2$ Azoxy-3-methyl-2-stilbazoles, 1699.
 $C_{28}H_{24}O_2N_2$ Ethylenedi-*O*-benzophenone oxime, 968.
 $C_{28}H_{28}O_2N$ 2-Amino-3:4-di-*tert*.-butylacenaphthenephthalanil, 744.
 $C_{28}H_{34}O_4S_2$ 3:4-Ditosyl tetra-acetyl mannitol, 1404.
 $C_{28}H_{34}O_2N_3$ Coprostan-6(β)-ol-3-one semicarbazone, 814.

28 IV

- $C_{28}H_{24}O_2N_2S_2$ Dithiobenzo-*p*-toluidide, 1234.
 $C_{28}H_{23}O_2BrS$ 2'(or 6')-Bromo-3':4'-di-*tert*.-butyl-1:7'-thionaphthenacenaphthenylindigo, 746.
 $C_{28}H_{23}O_2N_2P$ 3':5'-Benzylidene uridine-2' diphenyl phosphate, 340.

C₂₉ Group.

- $C_{29}H_{18}O_3$ Substance, from phenanthraquinone and methyleneanthrone, 998.
 $C_{29}H_{18}O_4$ Substance, from phenanthraquinone and benzylidenephthalide, 998.
 $C_{29}H_{22}O_8$ Dibenzoyl javanicin, 1027.
 $C_{29}H_{20}O_3$ 6(β)-Acetoxycoprostan-3(β)-ol, 814.

29 III

- $C_{29}H_{22}ON_2$ 4:4'-Dibenzylideneaminochalkone, 1419.
 $C_{29}H_{26}O_2N_2$ *pp'*-Bisbenzamidomethyldiphenylmethane, 1454.
 $C_{29}H_{28}O_2N_4$ 1:3-Bis-(*N*-phenyl-4-amidinophenoxy)propane, and its salts, 1116.
 $C_{29}H_{35}O_4N_5$ Oxodihydromethoxymethyldihydroeostrychnidine, 1555.

29 V

- $C_{29}H_{26}O_2ClBrS$ 5-Chloro-3-methyl-2'(or 5')-bromo-3':4'-di-*tert*.-butyl-1:7'-thionaphthenacenaphthenylindigo, 746.

C₃₀ Group.

- $C_{30}N_{46}$ Lanostatrienes, 1470.
 $C_{30}H_{50}$ α - and β -Lanostadienes, 1470.
 Squalene, reaction of sulphur with, 1546.

30 II

- $C_{30}H_{16}N_4$ Tetrakis-*p*-cyanophenylethylenc, 83.
 $C_{30}H_{21}Sb$ Tri- β -naphthylstibine, 1570.
 $C_{30}H_{28}O_2$ 7-Hydroxy-2':4'-dibenzoyloxy-3-methoxyflaven, 1684.
 $C_{30}H_{22}N_6$ 1:5-Naphthalenebisazo- β -naphthylamine, 81.
 $C_{30}H_{30}O$ Lanosterol, 1467.

30 III

- $C_{30}H_{20}O_2N_4$ 1:5-Naphthalenebisazo- β -naphthol, 81.
 $C_{30}H_{21}O_7Cl$ 7-Hydroxy-2':4'-dibenzoyloxy-3-methoxyflavylium chloride, 1684.
 $C_{30}H_{20}O_2N_2$ Benzylideneneobrucine, 80.
 $C_{30}H_{32}ON_2$ 2-Amino-3:4-di-*tert*.-butylacenaphthazo- β -naphthol, 744.

30 IV

- $C_{30}H_{27}O_4NS$ 3-Ethyl-2-(3':5'-di-*m*-methoxybenzoylpenta-2':4'-dienylidene)benzthiazoline, 1631.
 $C_{30}H_{24}O_6N_2S$ *NN'*-Dibenzoyl-1:2-bistoluene-*p*-sulphonamidoethane, 504.

C₃₁ Group.

- $C_{31}H_{23}O_2$ 2-(2':3'-Dihydro- β -naphthofuran-2')-2-phenyl- β -naphthopyran, 848.
 $C_{31}H_{24}O_4$ 2:2-Di-*p*-anisyl-3-methylphenanthro-9':10'-1:4-dioxen, 999.

31 IV

- $C_{31}H_{21}ClIA_3$ Phenyl-*m*-tolyl-*p*-phenyl-*p*-chlorophenylarsonium iodide, 510.
 Phenyl-*p*-tolyl-*p*-phenyl-*p*-chlorophenylarsonium iodide, 510.

31 V

- $C_{31}H_{27}O_4N_2IS_2$ Bis-2-(5:6-dimethoxy-3-ethylbenzthiazole)- $\beta\beta'$ -dimethylheptamethincyanine iodide, 962.
 1789

C₃₂ Group.

- C₃₂H₂₄N₂** Bis-2-(3:5-diphenylpyrrole)azamethin, 1200.
C₃₂H₂₄O₂ 2-(2':3'-Dihydro- β -naphthofuran-2')-2-*p*-tolyl- β -naphthopyran, 848.
C₃₂H₂₆O₂ 5:6-Diphenyl-(1'-methyl-7'-isopropylphenanthro)-9':10'-1:4-dioxen, 999.
C₃₂H₄₄O Di-(5-ethyltetradec-4-en-6-yl) ether, 758.

32 III

- C₃₂H₃₀O₂N₄** Bisquindolinoyl, 610.
C₃₂H₃₂O₂N₂ Dimethylaminoethyl hydrogen benzilate, 60.

32 IV

- C₃₂H₂₇ClAs** Phenyl-*p*-ethylphenyl-*p*-phenyl-*p*-chlorophenylarsonium iodide, 510.
C₃₂H₂₇N₃Cl₂S₂ [Bis-2-(3-ethylbenzthiazole)][$\alpha\beta'$ -dimethin-2'-(3'-ethylbenzthiazole)]trimethincyanine di-chloride, 1441.
C₃₂H₂₇N₃I₂S₂ [Bis-2-(3-ethylbenzthiazole)][$\alpha\beta'$ -dimethin-2'-(3'-ethylbenzthiazole)]trimethincyanine di-iodide, 1441.
C₃₂H₂₇N₃I₂Se₂ [Bis-2-(3-ethylbenzselenazole)][$\alpha\beta'$ -dimethin-2'-(3'-ethylbenzselenazole)]trimethincyanine di-iodide, 1442.

32 V

- C₃₂H₂₅N₃Cl₂I₂S₂** [Bis-2-(5-chloro-3-ethylbenzthiazole)][$\alpha\beta'$ -dimethin-2'-(5'-chloro-3'-ethylbenzthiazole)]tri-methincyanine di-iodide, 1442.
C₃₂H₂₅N₃Cl₂As₂Pd Dichlorobis(diphenyl-2-cyano-*n*-propylarsine)palladium, 622.

C₃₃ Group.

- C₃₃H₄₇ON** *O*-Hexylcholestenone oxime, 966.
C₃₃H₄₉ON *O*-Hexylcholestanone oxime, 966.

C₃₄ Group.

- C₃₄H₂₈O₂** Substance, from phenanthraquinone and 9-benzylidenexanthen, 998.
C₃₄H₂₈O₂ 2-(2':3'-Dihydro- β -naphthofuran-2')-2-phenyl-2':3-trimethylene- β -naphthopyran, 848.

34 III

- C₃₄H₂₀O₂N₂** Dodeca-5:7-diyne-4:9-diol bis- α -naphthylurethane, 1582.
C₃₄H₂₂O₂S Substance, from phenanthraquinone and 9-benzylidenethioxanthen, 998.
C₃₄H₂₆O₂N₂ Phthalobis-[γ -(6-methoxy-8-quinolylamino)propyl]amide, and its hydrochloride, 1334.
C₃₄H₄₁O₁₃N Substance, from 4:6-benzylidene 2:3-anhydro α -methylmannoside and ammonia, 20.

34 IV

- C₃₄H₂₀O₂N₂S₂** 1:2'-Bis-(3-keto-2-2'-quinolylthionaphthen), 1577.

C₃₅ Group.

- C₃₅H₂₄O₂** 2-(2':3'-Dihydro- β -naphthofuran-2')-2- α -naphthyl- β -naphthopyran, 848.

35 IV

- C₃₅H₃₃N₇I₂S₂** Bis-2-(3-ethyl-6:7-benzbenzthiazole)- $\beta\beta'$ -dimethylheptamethincyanine iodide, 962.

C₃₆ Group.

- C₃₆H₂₇O₂Sb** Tri-*p*-phenoxyphenylstibine, 1569.

36 IV

- C₃₆H₂₇O₂Cl₂Sb** Tri-*p*-phenoxyphenylstibine dichloride, 1570.
C₃₆H₂₇O₂Br₂Sb Tri-*p*-phenoxyphenylstibine dibromide, 1570.
C₃₆H₂₇O₂I₂Sb Tri-*p*-phenoxyphenylstibine di-iodide, 1570.
C₃₆H₃₀O₂N₂Sb₂ Bis(triphenylstibine)oxide dinitrate, 667.
C₃₆H₂₄O₂N₂As₂ *o*-Xylylene bis(phenyldimethylarsonium picrate), 665.

36 V

- C₃₆H₃₃O₁₄N₆ClAs₂** 4-Chloro-*o*-xylylene bis(phenyldimethyl arsonium picrate), 668.

C₃₇ Group.

- C₃₇H₃₁O₂Cl** *O*-5:2':4'-Tribenzoyl-*O*-3-methylmorinidin chloride, 1684.

C₃₈ Group.

- C₃₈H₂₈O₂** 2-(2':3'-Dihydro- β -naphthofuran-2')-2- α -naphthyl-2':3-trimethylene- β -naphthopyran, 848.

38 III

- C₃₈H₄₀O₂N₄** Tetraphenylethylenetetra-*p*-iminoethyl ether, 84.
C₃₈H₄₂O₂N₂ Substance, from diphenylketen dimer and piperidine, 176.

38 IV

- $C_{30}H_{14}O_2N_4Cl_2$ *l*-Tubocurarine chloride, 937.
 $C_{38}H_{12}O_{10}N_8S_4$ Tetrakis-*p*-amidinophenylethylene tetraisethionate, 84.

 C_{39} Group.

- $C_{39}H_{72}O_5$ $\alpha\alpha'$ -Dielaidin, 558.

 C_{40} Group.

- $C_{40}H_{20}O_2$ 2:2-Dixenylphenanthro-9':10'-1:4-dioxen, 999.
 $C_{40}H_{20}O_4$ 9-*m*-Tolylxanthyl peroxide, 1000.
 $C_{40}H_{16}O$ Mutachrome, pro-vitamin-*A* activity of, 131.

40 IV

- $C_{40}H_{14}O_2N_4Br_2$ 1:1'-Dibromo-3:3'-dinaphthyl-2:2'-bisazo- β -naphthol, 1392.
 $C_{40}H_{18}O_2N_2I_2$ 1-*O*-Methyltubocurarine iodide, 937.

 C_{41} Group.

- $C_{41}H_{30}O_2$ 2:2-Dixenyl-3-methylphenanthro-9':10'-1:4-dioxen, 999.

 C_{42} Group.

- $C_{42}H_{14}O_3As_2$ Bisphenyl-*p*-tolyl-*p*-ethylphenylarsine oxide-dihydroxide, 509.

 C_{44} Group

- $C_{44}H_{37}N_3I_2S_3$ [Bis-2-(3-ethyl-6:7-benzbenzthiazole)][$\alpha\beta'$ -dimethin-2'-(3'-ethyl-6:7'-benzbenzthiazole)]trimethincyanine di-iodide, 1441.

 C_{45} Group.

- $C_{45}H_{12}O_5$ 2-Methyl 3:5-ditrityl methylxylofuranoside, 850.

 C_{46} Group.

- $C_{46}H_{12}O_6$ 2-Acetyl 3:5-ditrityl methylxylofuranoside, 850.

46 III

- $C_{46}H_{30}O_2S_2$ 9- α -Naphthylthioxanthyl peroxide, 1000.

 C_{52} Group.

- $C_{52}H_{32}O_4Cl_2As_2Pd$ Dichlorobis(phenylbis-3-benzyloxypropylarsine)palladium, 624.

 C_{66} Group.

- $C_{66}H_{16}O_4Cl_6As_2Pt$ Phenylbenzylbis-3-benzyloxypropylarsonium chloroplatinate, 624.

SYMBOLS FOR THERMODYNAMICAL AND PHYSICO-CHEMICAL QUANTITIES AND CONVENTIONS RELATING TO THEIR USE, ADOPTED AS RECOMMENDED PRACTICE BY THE CHEMICAL SOCIETY.

(Where two or more symbols separated by commas or semicolons are given for a quantity, these symbols are to be regarded as alternatives for which no preference is expressed. On the other hand, where two symbols are separated by a dotted line, the former is the first preference.)

1. To be Printed in Black Italic.

(Certain important physical constants.)

F	Faraday's constant.
J	Mechanical equivalent of heat.
N	Avogadro's number.
R	{ Gas constant per mol. Rydberg's constant.
c	Velocity of light in vacuo.
e	Electronic charge (charge equal and opposite in sign to that of an electron).
g	Acceleration due to gravity (standard value, if variation from standard is significant).
h	Planck's constant.
k	Boltzmann's constant.
m	Rest mass of an electron.

2. To be Printed in Ordinary Italic, when not Greek.

General Physics and Chemistry.

Length	l
mean free path of molecules	l
height	h
diameter, distance	d
diameter of molecules	σ
radius	r
Mass	m
molecular weight	M
atomic weight	A
atomic number	Z
gram-equivalent weight	Z, J
Time	t
time interval, especially half- or mean-life	τ
frequency	ν
Velocity	$v; c, (u, v, w)$
of ions	u (with subscript)
angular	ω
Acceleration	$f a$
due to gravity (as variable)	g
Force	$F, (X, Y, Z)$
Moment of inertia	I
Pressure	p, P
especially osmotic	Π
Volume	v, V
Density	ρd
Compressibility	κK

Viscosity	η
Fluidity	ϕ
Surface area	A s
Angle of contact	θ
Surface tension	γ σ
Parachor	$[P]$
Surface concentration excess	Γ
Number of mols	n
Concentration, mol fraction	N, x
in other terms	c, C
Solubility	s
Diffusion coefficient	D
Chemical equilibrium constant (products/reactants)	K
solubility product	K_s L
Velocity constant of chemical reaction	k
Number of molecular collisions per second	Z
Partition function	f
Efficiency, of any process	η
Wave function	ψ

Heat and Thermodynamics.

Temperature, on absolute scale, ($^{\circ}\text{K}$)	T
on other scales	θ t
Thermal conductivity	k
Energy (general symbol)	E
Work done by or on a system	w W
Heat entering a system	q
Specific heat	c_p and c_v
molecular heat	C_p and C
Ratio of specific heats	γ
Latent heat, per g.	l
per mol	L
Intrinsic energy	U E
Enthalpy, total heat, or heat content	H
Entropy	S
Free energy (Helmholtz)	A F
Thermodynamic potential, Gibbs function, free	
energy (G. N. Lewis)	G
Vapour pressure constant	i
Chemical potential	μ
Activity	a
coefficient (for molar concentration)	f
Osmotic coefficient	g
Van 't Hoff's factor	i

Electricity.

Quantity of electricity	Q
especially electrostatic charge	e
Potential (difference)	} V
Volta potential	
electrokinetic potential	ζ
especially electromotive force of voltaic cells	E
Potential gradient, in electric field	X
Electronic exit work function	ϕ

Current	I
Resistance	R
specific resistance	ρr
specific conductance	$\kappa \sigma$
Inductance, self	L
mutual	M
Electrostatic capacity	C
Dielectric constant	ϵ
Dipole moment	μ

Electrochemistry.

Degree of electrolytic dissociation	α
Valency of an ion	z
Ionic strength	I
Equivalent conductance	Λ
equivalent ionic conductance, "mobility"	l (with subscript)
Transport number	T (with subscript)
	n (with subscript)
Single electrode potential	e (with subscript),
	E (with subscript)
Electrolytic polarisation, overvoltage	$\eta \pi$

Magnetism.

Magnetic field strength	H
flux	ϕ
permeability	μ
susceptibility—volume	κ
mass	χ
moment	M
induction	B

Optics.

Wave length	λ
Wave number	ν
Intensity of light	I
Refractive index	n (with subscript)
	μ (with subscript)
specific refraction	r (with subscript)
molecular refraction	$[R]$ (with subscript)
Molar extinction coefficient	ϵ
Angle of (optical) rotation	α
specific rotation	$[\alpha]$
Specific magnetic rotation	ω

3. To be Printed in Roman, when not Greek.*(a) Examples of Mathematical Constants and Operators.*

Base of natural logarithms	e
Ratio of circumference to diameter	π
Differential	d
partial	∂
Increment	Δ
very small increment	δ
Sum	Σ
Product	Π
Function	f, ϕ

(b) *Examples of single-letter abbreviations.*

*Ampère (in sub-units)	a.
Volt	v.
Ohm	Ω .
Watt	w.
Farad	F.
Henry	H.
Centigrade	C.
Fahrenheit	F.
Kelvin	K.
Ångstrom unit	Å.
micron	μ .
metre	m.
gram	g.
litre	l.
Röntgen unit	r.
†Normal (concentration)	N.
†Molar (concentration)	M.

The following prefixes to abbreviations for the names of units should be used to indicate the specified multiples or sub-multiples of these units :

M	mega-	$10^6 \times$
k	kilo-	$10^3 \times$
d	deci-	$10^{-1} \times$
c	centi-	$10^{-2} \times$
m	milli-	$10^{-3} \times$
μ	micro-	$10^{-6} \times$

e.g., M Ω . denotes megohm; kw., kilowatt; and μ g., microgram. The use of $\mu\mu$. instead of m μ . to denote 10^{-7} cm., or of γ to denote microgram is deprecated.

4. Subscripts and other Modifying Signs.

(a) *Subscripts to symbols for quantities.*

$I, II \dots$	{ especially with symbols for thermodynamic functions, referring to different systems or different states of a system.
$I, 2 \dots$	
A, B \dots	referring to molecular species A, B, etc.
i	referring to a typical ionic species i .
u	referring to an undissociated molecule.
+,	referring to a positive or negative ion, or to a positive or negative electrode.
p, v, T	indicating constant pressure, volume, and temperature respectively.
q	indicating adiabatic conditions.
w	indicating that no work is performed.
p, c, a	with symbol for an equilibrium constant, indicating that it is expressed in terms of pressure, concentration, or activity.
G, V, L, X	referring to gas, vapour, liquid, and crystalline states, respectively.
f, e, s, t, d	referring to fusion, evaporation (vaporisation of liquid), sublimation, transition, and dissolution or dilution respectively.
c	referring to the critical state or indicating a critical value.
∞	referring to a standard state, or indicating limiting value at infinite dilution.

* *E.g.* "ma." for "milliampère"; but "amp." is preferred for "ampère."

† Separated by a hyphen (and no full stop) from a chemical formula which follows it.

C, D, F *with symbols for optical properties, referring to a particular wavelength.*

Where a subscript has to be added to a symbol which already carries a subscript, the two subscripts may be separated by a comma or the symbol with the first subscript may be enclosed in parentheses with the second subscript outside.

(b) *Other modifying signs.*

- o *as right-hand superscript to symbol (particularly to a symbol for a general thermodynamic function—see p. 1795), referring to a standard state.*
- [] *enclosing formula of chemical substance, indicating its molar concentration.*
- { } *enclosing formula of chemical substance, indicating its molar activity.*

In crystallography it is recommended that :

Millerian indices be enclosed in parentheses, () ;

Laue indices be unenclosed ;

Indices of a plane family be enclosed in braces, { } ;

Indices of a zone axis or line be enclosed in brackets, [] .

Numerals attached to a symbol for a chemical element in various positions have the following meanings :

upper left mass number of atom.

lower left nuclear charge of atom.

lower right number of atoms in molecule.

e.g., ${}^7\text{Li}$; ${}^2\text{H}_2$ (= D_2).

ALPHABETICAL INDEX OF RECOMMENDED SYMBOLS, and single-letter abbreviations.

including all those given in the above lists except prefixes, subscripts and other modifying signs.

The name of any quantity for which a given symbol is a second preference is printed in parentheses.

- A free energy—Helmholtz ; atomic weight ; surface area.
- Å. Ångstrom unit.
- a activity ; (acceleration).
- a. ampère, in sub-units—see footnote, p. 988.
- B magnetic induction.
- C concentration ; electrostatic capacity.
 with subscript : molecular heat capacity.
- c. Centigrade.
- c velocity of light in vacuo.
- c velocity ; concentration.
 with subscript : specific heat.
- D diffusion coefficient.
- d diameter ; distance ; (density).
- d differential.
- ∂ partial differential.
- E energy ; (intrinsic energy) ; potential difference, especially electromotive force of voltaic cells.
 with subscript : single electrode potential.
- e electronic charge—charge equal and opposite in sign to that of an electron.
 quantity of electricity, especially electrostatic charge.
 with subscript : single electrode potential.

- e** base of natural logarithms.
F Faraday's constant.
F force; (free energy—Helmholtz).
F. farad; Fahrenheit.
f acceleration; activity coefficient, for molar concentration; partition function.
f function.
G thermodynamic potential, Gibbs function, free energy—G. N. Lewis.
g acceleration due to gravity, standard value.
g acceleration due to gravity, as a variable; osmotic coefficient.
g. gram.
H enthalpy, total heat, heat content; magnetic field strength.
H. henry.
h Planck's constant.
h height.
I moment of inertia; ionic strength; electric current; intensity of light.
i vapour pressure constant; van 't Hoff's factor.
J mechanical equivalent of heat.
J gram-equivalent weight.
K chemical equilibrium constant; (compressibility).
K, solubility product.
K. Kelvin.
k Boltzmann's constant.
k thermal conductivity; velocity constant of chemical reaction.
L latent heat per mol; self inductance; (solubility product).
l latent heat per g.; length; mean free path of molecules.
with subscript: equivalent ionic conductance, "mobility".
l. litre.
M molecular weight; mutual inductance; magnetic moment.
M. molar concentration.
m rest mass of an electron.
m mass.
m. metre.
N Avogadro's number.
N mol fraction.
N. normal concentration.
n number of mols.
with subscript: (transport number).
with subscript: refractive index.
P pressure.
[P] parachor.
p pressure.
Q quantity of electricity.
q heat entering a system.
R gas constant per mol; Rydberg's constant.
R electrical resistance.
[R] *with subscript*: molecular refraction.
r radius; (specific resistance).
with subscript: specific refraction.
r. Röntgen unit.
S entropy.
s solubility; (surface area).
T temperature, on absolute Kelvin scale.
with subscript: transport number.
t time; (temperature—not on absolute scale).
U intrinsic energy.

u	velocity component. <i>with subscript</i> : velocity of ions.
V	volume; potential, potential difference, including Volta potential.
v	volt.
v	volume; velocity; velocity component.
W	(work done by or on a system).
w	watt.
w	work done by or on a system; velocity component.
X	force component; potential gradient in electric field.
x	mol fraction.
Y	force component.
Z	force component; g.-equivalent weight; number of molecular collisions per second; atomic number.
z	valency of an ion.
α	degree of electrolytic dissociation; angle of optical rotation.
$[\alpha]$	specific optical rotation.
Γ	surface concentration excess.
γ	ratio of specific heats; surface tension.
Δ	increment.
δ	very small increment.
ϵ	dielectric constant; molar extinction coefficient.
ζ	electrokinetic potential.
η	efficiency of any process; viscosity; electrolytic polarisation, overvoltage.
θ	angle of contact; temperature—not on absolute scale.
κ	compressibility; specific conductance; magnetic susceptibility—volume.
Λ	equivalent conductance.
λ	wave length.
μ	chemical potential; dipole moment; magnetic permeability. <i>with subscript</i> : (refractive index).
μ	micron.
ν	frequency; wave number.
Π	pressure, especially osmotic pressure.
Π	product.
π	(electrolytic polarisation, overvoltage).
π	ratio of circumference to diameter.
ρ	density; specific resistance.
Σ	sum.
σ	diameter of molecules; (surface tension); (specific conductance).
τ	time interval, especially half or mean life.
ϕ	fluidity; electronic exit work function; magnetic flux.
Φ	function.
χ	magnetic susceptibility—mass.
ψ	wave function.
Ω	ohm.
ω	angular velocity; specific magnetic rotation.

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